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Editorial

Thromboangiitis Obliterans: Fact or Fancy

IN A RECENT publication the entire experience with Buerger's disease at the Beth Israel Hospital in Boston was analyzed and the various considerations that have perpetuated it as an entity were reviewed.[1] It was concluded from this study that the disease originally described by Buerger is indistinguishable from atherosclerosis, systemic embolization, or peripheral arterial or venous thrombosis, singly or in combination. Because of the difficulties inherent in establishing a negative hypothesis, any attempt to prove that thromboangiitis obliterans does not exist can approach such a goal only asymptotically. To this observer, however, an impartial examination of the entire evidence provides overwhelming support for the opinion that Buerger's disease has never been and is not now an entity in either the clinical or pathologic sense.

The more carefully one examines the various factors associated with the diagnosis of Buerger's disease, the less convincing they appear. In view of current knowledge of the relative frequency of atherosclerosis among young men, it is no longer reasonable to consider age and sex as distinguishing features of Buerger's disease. To appreciate how this association may initially have come about, however, it is necessary to recall that Buerger's original investigations were completed in an era when neither the frequency of clinically significant atherosclerosis nor the ubiquity of thromboembolism was fully recognized. Herrick's classic treatise on the correlation of the pathology of coronary occlusion with the clinical picture of myocardial infarction, for example, was first published 4 years after Buerger described the disease that bears his name. Buerger's initial studies also preceded by several decades the extensive observations on the high incidence of coronary atherosclerosis in young men. Although the use of tobacco and the presence of clinical phlebitis have been considered important findings in the diagnosis of Buerger's disease, no reports were uncovered in which these relationships were established through the use of control studies. It is now also clear that the secondary and tertiary lesions of thromboangiitis obliterans are nonspecific and may result from arterial obstruction from any cause, and that the extent of perivascular fibrosis is no greater in thromboangiitis obliterans than in other thrombotic disorders.

Since the etiology is unknown, the clinical features of the disease are not diagnostic, and the intermediate and healed morphologic lesions are nonspecific, validation of the disease as an entity must rest, finally, with the acute lesion, which Buerger considered to be "absolutely diagnostic." The acute vascular lesion has occasionally been described in superficial veins, but only rarely in deep veins or in arteries. The paucity of such acute lesions in

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the deep vessels has usually been attributed to the fact that the affected limbs are amputated only in the late stages of the disease. However, if the natural history of Buerger's disease is indeed that of an episodic, recurrent, and relapsing process, it is remarkable that the traces of the acute lesion are reported so rarely in these specimens. This is particularly significant, since recent arterial thrombi devoid of acute inflammatory reaction have often been noted in such amputated specimens. Although the literature contains a few photomicrographs that resemble in part the picture described by Buerger, it is often difficult to determine whether the vessel is an artery or a vein, whether the wall is intact, whether the surrounding area is free of infection, or even whether or not a septic endocarditis may have been present. Of particular interest in this regard were Buerger's own photomicrographs relating to the acute arterial lesions as documented in five of his major reports. There are four separate examples in which the identical photomicrographs, allowing for minor differences in photographic contrast, spatial orientation, and magnification, are labeled a vein in early papers and an artery in subsequent ones. This identity takes on greater significance since these lesions, together with an additional lesion shown only once, seem, in fact, to be veins rather than arteries.[1] The reader is forced to the conclusion that, although Buerger may indeed have seen an acute arterial lesion, he did not at any time present documentary proof of its existence.

Fortunately, the issue of the identity of thromboangiitis obliterans does not, in the final analysis, turn on the inconclusive evidence of whether or not an acute arterial lesion has been seen. It rests, rather, on the *specificity* of this acute vascular lesion, a question that, for want of adequate arterial lesions, can best be approached in the vein, where the morphologic findings are well documented. From the pathologic point of view, specificity is based on such features as inflammation without necrosis and the presence of giant cells within the thrombus. As shown in control venous biopsies,[1] however, the degree of reactive inflammation may vary greatly and may occasionally be as marked as that observed by Buerger. The specificity of the lesion cannot rest on the presence of giant cells alone, since these vary from section to section, may be entirely absent from some areas and can, moreover, be found occasionally in recently organizing thrombi.

There are now sufficient data concerning the morphologic response of arteries and veins in many pathologic processes to indicate clearly that the arterial response does not necessarily mimic the venous reaction. Even granting the existence of a comparable lesion in arteries, however, one must be able to justify the calling of such a lesion specific in the absence of a definitive clinical picture or pathognomonic, morphologic, or etiologic components. It is only necessary to recall the relation of the sarcoid lesion to sarcoidosis or the Aschoff body to rheumatic fever to indicate how difficult it is to find an "absolutely diagnostic" lesion on pathologic grounds alone. If, in addition, one recognizes that the lesion may be mimicked in whole or in part by other less specific processes and that the evidence for its actual existence is tenuous at best, there seems little justification for permitting the whole case for thromboangiitis obliterans to rest entirely on this lesion.

Skepticism concerning the identity of thromboangiitis obliterans has been expressed by numerous investigators,[2–5] and other observers have indicated their failure to find examples of the disease among varied hospital populations. Yet, there remains today a widely held belief that thromboangiitis obliterans is a distinct, if uncommon, disease. Retention of thromboangiitis as an entity has been urged by some investigators because, in their opinion, the diagnosis of Buerger's disease describes a characteristic and recognizable clinical picture. Such findings, however, do not define a disease. Others persist in the belief that thromboangiitis obliterans exists because the symptoms and signs respond to specific therapy. Yet, there is no evidence from controlled clinical trials that any ther-

apy, including abstinence from tobacco, is more beneficial to patients said to have Buerger's disease than to patients of similar age with established forms of peripheral arterial insufficiency of comparable severity. Finally, some observers insist that the existence of an acute pathognomonic vascular lesion justifies acceptance of thromboangiitis obliterans as an entity. These same observers explain the paucity of specific arterial lesions on the fact that the disease is no longer as common as it once was. As indicated above, the specificity of the acute vascular lesion has never been established, and the data provided by Buerger's own photomicrographs lend no credence to the belief that the disease was seen more commonly before than after World War II.

This editorial will perhaps serve its most useful function, if these comments stimulate those physicians who still believe in the entity of Buerger's disease to review critically their own experiences with thromboangiitis obliterans.

STANFORD WESSLER

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Whether my observations and opinions be disproved or supported, I shall be equally satisfied. Truth is the prize aimed for; and, in the contest, there is at least this consolation, that all the competitors may share equally the good attained.—DOMINIC JOHN CORRIGAN, M.D. *The Lancet* 1:586, 1829.

Essential Hypertension and Aldosterone

By ELEANOR H. VENNING, PH.D., INGE DYRENFURTH, PH.D., JOHN B. DOSSETOR, B.M. (Oxf.), AND JOHN C. BECK, M.D.

MANY FACTORS have been implicated in the etiology of essential hypertension and at present the primary cause of this disease remains obscure. The relationship of sodium to the development of hypertension and the question of involvement of the adrenal cortex has been the subject of numerous investigations. Efforts by earlier investigators to show a hypersecretion of corticosteroids in this condition were conflicting and the general conclusions were that there was no consistent abnormality in adrenal cortical function in this disease. With the isolation of aldosterone, a highly active, naturally occurring sodium-retaining hormone, interest has been renewed in the relationship of the adrenal cortex to hypertension. An elevated blood pressure is the usual finding in patients with primary aldosteronism,[1] and the administration of aldosterone to normal individuals and to patients with Addison's disease over periods of 2 to 3 weeks results in a rise in blood pressure.[2,3] Genest et al.[4-6] have reported that 55 per cent of patients with essential, renal, and malignant hypertension, excrete amounts of aldosterone in the higher range or above normal levels. In a more recent study, using an isotope-dilution technic, Laragh and co-workers[7] found the secretion rate of aldosterone to be within the normal range in patients with benign essential hypertension. In hypertensive patients with renal or vascular complications, the secretion was significantly increased.

In the present study a survey was made of the levels of urinary aldosterone and its reduced metabolite in normal individuals and in patients with essential hypertension in whom the sodium intake was known. A small group of patients with malignant and renal hypertension was also investigated. Most of the patients were followed from 2 to 6 days in the hospital. The response of plasma and urinary 17-hydroxycorticosteroids and urinary aldosterone to the administration of adrenocorticotrophic hormone (ACTH) was investigated and in addition the steroid content of the adrenal glands obtained at autopsy from two patients with malignant hypertension was determined.

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Methods

Aldosterone was extracted from urine after hydrolysis at pH 1.5 at room temperature for 48 hours. The fraction containing aldosterone was purified on paper in four chromatographic systems as outlined by Dyrenfurth and Venning[8] and was measured by reduction with blue tetrazolium.

The tetrahydro derivative of aldosterone was hydrolyzed by means of β-glucuronidase and was isolated and determined after acetylation by the reduction of blue tetrazolium according to a modification of the procedure of Ulich and Lieberman.[9] The details of this method will be published by Dyrenfurth et al.[10]

Urinary 17-hydroxycorticosteroids were determined by the Porter-Silber method[11] and the plasma 17-hydroxycorticosteroids by the method of Bush and Silber.[12] The pattern of corticosteroid excretion was examined in two patients with essential hypertension, and the steroid content of adrenal tissue from two patients with malignant hypertension by procedures previously outlined by Dyrenfurth and co-workers.[13, 14]

The functional capacity of the adrenal gland to respond to the administration of adrenocorticotrophic hormone was determined in 5 patients with essential hypertension and was compared with responses obtained in normotensive individuals.[15]

The normal subjects and the hypertensive patients were studied either in the metabolic unit or in the general medical wards of the Royal Victoria Hospital. In the former instance complete metabolic balance technics were followed and the dietary composition was determined from food tables with periodic checking of sample diets. The dietary intake of patients studied on the general wards was supervised by a dietitian who calculated the

electrolyte content on the basis of the actual daily food intake.

Clinical Material

It has been customary to classify hypertension into a primary and a secondary form, the former being largely a diagnosis of exclusion. The patients described in this study were carefully investigated from the clinical point of view. Meticulous inquiry into the family history as well as into a previous history of renal disease was made. In all patients urinalysis and routine hematologic studies were performed as well as an electrocardiogram, a radiologic examination of the chest, and an intravenous pyelogram. Nonprotein nitrogen or serum creatinine, serum sodium, potassium, chloride, and bicarbonate determinations were carried out in all patients. In most of the individuals studied a phentolamine (Regitine) test was carried out as a screening procedure for pheochromocytoma, as well as a tetraethyl ammonium chloride test (TEAC) as a screening procedure for unilateral renal vascular disease. Urinary catecholamines were determined when indicated, as were repeated urine cultures when clinical or laboratory evidence suggested the presence of a pyelonephritis. In many patients an endogenous creatinine clearance, as an index of glomerular filtration rate, was determined, as well as a 10 ml. intravenous phenolsulfonphthalein test with collection of urines at 15, 30, 60, and 120 minutes. In patients in whom hypertension secondary to a unilateral renal vascular lesion was suspected, aortography and differential renal function studies as described by Howard[23] were performed. Although the pitfalls of any attempt to classify patients with hypertension are well recognized, it was considered that there was some merit in subdividing these hypertensive subjects into the following categories:

1. Essential hypertension without clinical and laboratory evidence of renal disease.

2. Essential hypertension with renal disease. These were patients with a previous diagnosis of essential hypertension who developed laboratory evidence compatible with arteriolar nephrosclerosis.

3. Hypertension secondary to renal disease. These patients had previously recognized glomerulonephritis, pyelonephritis, or periarteritis nodosa. A clear-cut separation of categories 2 and 3 may be impossible in some patients with the clinical laboratory procedures available at the present time.

4. Malignant hypertension. These individuals had an accelerated form of hypertension associated with progressive renal damage, retinopathy, and papilledema.

The distinctions made in these four categories were based on the belief that they probably represent a progressive advance in the severity of the disease. There is as yet a lack of information concerning the effect of alterations in renal functional capacity upon aldosterone excretion by the adrenal cortex.

5. Hypertension associated with generalized arteriosclerosis.

6. Hypertension with associated heart failure. This group was separated because it was thought that the syndrome of congestive heart failure in itself elevates the urinary aldosterone excretion.

7. Hypertension associated with pheochromocytoma.

The sodium intake in these cases was controlled but only a limited number were placed on complete metabolic studies, the results of which will be reported in a subsequent communication.

The clinical report of the two cases with malignant hypertension whose adrenal glands were analyzed for their steroid content (table 1) is as follows:

Case 1 was an obese man, aged 42 years, with severe hypertension, who had been treated for several months with reserpine, chlorothiazide, and a low-sodium diet. Since he was unreliable, he probably did not follow his treatment. He suffered a cerebral hemorrhage, was admitted to the hospital in an unconscious state, and died that night. An autopsy was performed 20 hours after death and showed the following pathologic changes: subarachnoid hemorrhage, hypertrophy and dilatation of the heart, malignant nephrosclerosis, arteriolar sclerosis and necrosis of the adrenal glands, liver, and spleen, and adrenal cortical hyperplasia, nodular in part.

Case 2 was a woman aged 53 years, with a history of severe hypertension for at least 6 months,

Table 1

Steroid Content of Adrenal Glands in Malignant Hypertension

	Adrenal weights					
	Left (Gm.)	Right (Gm.)	Hydrocortisone (μg./Gm.)	Cortisone (μg./Gm.)	Aldosterone (μg./Gm.)	Corticosterone (μg./Gm.)
Case 1, male	7.4	—	0.9	1.1	2.6	2.1
Case 2, female	10.3	17.1 (+)	3.3	4.0	2.9	2.4

Table 2

Excretion of Aldosterone in Hypertension

Cases	No. of cases	No. of assays	Sodium intake (mEq./24 hrs.)	Aldosterone — μg./24 hr. Range	Mean	S.E.
Normotensive Individuals	72	114	100-170	2.0-12.0	5.1	0.22
1. Essential hypertension	22	72	100-150	3.3-18.9	8.8	0.43
without renal disease	4	19	70- 85	5.7-19.6	12.0	1.14
2. Essential hypertension	5	14	100-150	5.4-14.3	10.1	0.88
with renal disease	1	4	70- 85	13.8-18.7	15.4	
3. Hypertension secondary to renal disease	4	11	100-150	11.7-29.0	19.4	1.75
4. Malignant hypertension	2	4	100-150	12.0-18.0	15.0	
	2	7	70- 85	18.5-29.2	23.3	
5. Hypertension and arteriosclerosis	2	6	100-150	2.5- 9.3	5.7	
6. Hypertension and	1	3	100-150	5.8- 8.0	7.0	
heart failure	1	5	70- 85	11.6-18.7	14.7	
7. Pheochromocytoma	2	2	100-150	4.0- 7.1	5.6	

congestive heart failure, and pyelonephritis. Her blood pressure did not respond to hypotensive drugs. She developed hypokalemia on chlorothiazide and the sodium intake was reduced to 86 mEq. per day with supplementary potassium chloride, 2.5 mg. of mecamylamine hydrochloride daily, and frequent mersalyl injections. After a week on this therapy she was discharged. She was readmitted 2 days later following a fall. At this time serum electrolytes were within normal range. On the second day the blood pressure dropped and convulsions occurred, and an emergency neurosurgical procedure was performed. This was followed on the third day by a tracheotomy. The patient died that night. An autopsy performed 10 hours after death showed brain contusion and laceration with subdural hemorrhage, severe bilateral chronic pyelonephritis with marked vascular sclerosis, hypertrophy of the heart, and hyperplastic adrenal glands with a large adenoma of the right adrenal gland.* There was no clinical evidence to suggest that this might have been a case of primary aldosteronism nor did the patient show any symptoms of Cushing's syndrome.

*We are indebted to Dr. Sean Moore of the Department of Pathology, Montreal General Hospital, for the supply of adrenal tissue.

Results

The results of the survey are shown in table 2. Forty-six patients with hypertension were studied and a total of 147 assays of aldosterone was made. Twenty-six of these patients presented a picture of essential hypertension without clinical and laboratory evidence of renal disease. They were divided into two groups, depending upon their sodium intake. This varied from 100 to 150 mEq. per day in the first group and from 70 to 85 mEq. per day in the second group. In the normotensive group the estimated sodium intake was between 100 and 170 mEq. per day.

The healthy individuals excreted amounts of aldosterone ranging from 2 to 12 μg. per day, with a mean value of 5.1 ± S.E. 0.22. The patients with essential hypertension showed values ranging from 3.3 to 18.9 μg. per day, with a mean value of 8.8 ± S.E. 0.43. The difference between these two means was statistically significant, $p < 0.001$. A distribution curve of the urinary aldosterone values

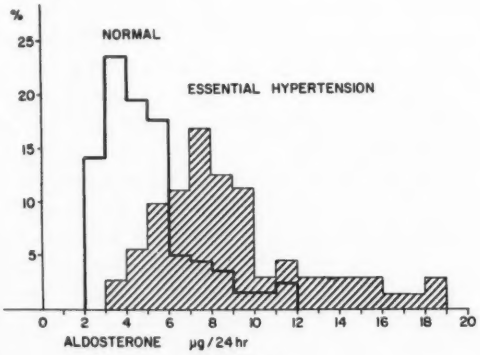

Figure 1

Distribution of 24-hour excretion rates of aldosterone in normotensive individuals and patients with essential hypertension.

in normotensive individuals and in patients with essential hypertension is shown in figure 1. Approximately 75 per cent of the normal subjects showed values between 2 and 6 µg. per day whereas 82 per cent of the patients with essential hypertension excreted amounts greater than 6 µg. aldosterone per day.

In four patients with essential hypertension in whom the sodium intake had been restricted to 70 to 85 mEq. per day, the urinary aldosterone values ranged from 5.7 to 19.6 µg. per day, with a mean value of 12.0 ± S.E. 1.14 µg.

The patients with essential hypertension and secondary renal disease, on a normal sodium intake, showed a higher mean value of 10.1 ± S.E. 0.88 µg. per day than those with benign essential hypertension, and in the group in which the hypertension was associated with primary renal disease the mean value was 19.4 ± S.E. 1.75 µg.

Prior to the collection of urine, the patients with malignant hypertension had been in the hospital for a few weeks and had received ganglion-blocking agents and reserpine in an effort to control the blood pressure. In two patients on a normal sodium intake the mean value for aldosterone excretion was 15.0 µg. per day, whereas that obtained in two patients on a lower sodium intake was 23.3 µg. Two older women, aged 68 and 72 years, with mild hypertension and arteriosclerosis, had values for urinary aldosterone within the normal

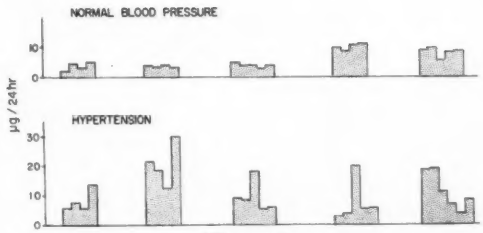

Figure 2

Fluctuations in daily urinary aldosterone levels in normal subjects and in patients with essential hypertension on a known sodium intake.

range and one patient with hypertension and heart failure also showed a normal output of aldosterone. A second patient in this group on a sodium intake of 70 to 85 mEq. had values ranging from 11.6 to 18.7 µg. per day. In the two patients with proved pheochromocytoma, the aldosterone output was within the normal range.

In each group of hypertensive patients the mean aldosterone excretion was always higher with the lower sodium intake. In general the severity of the disease tended to be greater, so that it is perhaps not justifiable to attempt to assess the influence of the lower sodium intake on aldosterone excretion in these cases.

When hypertensive patients were followed daily for periods of 4 to 6 days, it became evident that many showed wider fluctuations in aldosterone excretion than normotensive individuals. Approximately 30 per cent of the cases studied showed these fluctuations. The daily aldosterone excretions in five hospitalized normotensive and five hypertensive subjects that showed these fluctuations are depicted in figure 2.

The amount of aldosterone extracted from urine at pH 1.5 represents only a small fraction of the amount elaborated by the adrenal gland. Part of the hormone is metabolized in the body and is excreted as a tetrahydro derivative. The values found by Dyrenfurth and co-workers[10] in 34 normotensive persons (17 males and 17 females) was 23.1 µg. ± S.E. 1.49 (ranges 6.8 to 38 µg.) In 11 determinations carried out on seven patients with essential hypertension on a normal sodium

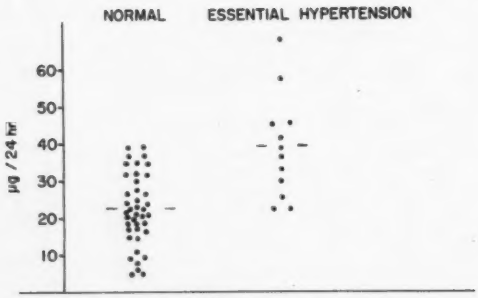

Figure 3

Excretion of tetrahydro metabolite of aldosterone in normal individuals and patients with essential hypertension.

intake the values ranged from 22.3 to 66.7 µg. per 24 hours, with a mean value of 38.4 ± S.E. 4.3 (fig. 3).

The daily excretion of aldosterone and its metabolite is shown for two patients with hypertension in table 3. Case 1, a man, age 40 years, with chronic glomerulonephritis and hypertension was receiving a sodium intake of 100 mEq. per day. Despite treatment with hydralazine the patient's blood pressure stayed at a mean of 210/110 mm. Hg. At the time of the assays the nonprotein nitrogen and edema were increasing and the patient died 6 days later. With deterioration in the patient's condition, the levels of urinary aldosterone rose from 11.7 to 28.7 µg. and its metabolite from 68.9 to 185 µg. per day.

A second case, a man, age 41 years, with malignant hypertension, was followed for 10 days. One week prior to admission to the hospital a subarachnoid hemorrhage had occurred and the blood pressure at that time was 204/130. Bilateral grade IV hypertensive retinopathy was present. The patient was given a 10 mEq. sodium diet; reserpine and hydralazine were administered. The blood pressure fluctuated considerably during the first 3 weeks and finally reasonably good control was achieved with reserpine, 0.2 mg. three times a day by mouth and hydralazine every 6 hours in alternating doses of 50 and 75 mg. The assays were carried out after relative control of the blood pressure had been achieved at a level of 140/90. At the beginning of the study, both aldosterone and its metabolite were excreted at high levels and gradually decreased although the low-sodium intake was maintained throughout. During this period there was also an improvement in the patient's clinical condition although the blood pressure changes could not be correlated with the level of aldosterone excretion.

Table 3

Excretion of Aldosterone and Its Metabolite in Patients with Hypertension and Renal Disease

Case	Sodium intake (mEq./24 hr.)	Treatment	Blood pressure (mm.Hg)	Aldosterone (µg./24 hr.)	Aldosterone metabolite (µg./24 hr.)
1. Glomerulonephritis	100	apresoline	210/110	11.7	68.9
	100	apresoline		18.7	112.0
	100	apresoline		28.7	185.0
2. Malignant hypertension*	10	reserpine & apresoline	135/82	29.8	124.2
	10	reserpine & apresoline	135/82	19.8	142.3
	10	reserpine & apresoline	138/110	28.0	174.9
	10	reserpine & apresoline	150/100	14.1	165.6
	10	reserpine & apresoline	140/90	24.0	125.0
	10	reserpine & apresoline	148/88	18.0	144.0
	10	reserpine & apresoline	150/85	14.8	67.3
	10	reserpine & apresoline	165/100	11.2	62.0
	10	reserpine & apresoline		9.3	46.0
	10	reserpine & apresoline	172/100	18.0	70.0

*On admission to hospital blood pressure was 240/130. Assays were carried out 3 weeks later during continued therapy.

Excretion of 17-Hydroxycorticosteroids

The excretion of 17-hydroxycorticosteroids measured by the Porter-Silber method in patients with essential hypertension was within the range observed in healthy individuals and was not affected by hospitalization (table 4). In two patients with this disease the corticosteroids were fractionated on paper and a pattern was obtained of the ultraviolet-absorbing and blue tetrazolium-reducing urinary corticosteroids. The patterns were essentially normal. Figure 4 shows the results obtained on a woman, age 63 years, when maintained on a normal and a low-sodium intake and also following the administration of adrenocorticotrophin.

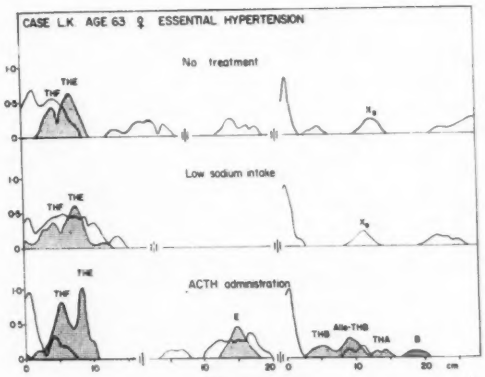

Figure 4

Pattern of excretion of corticosteroids in a patient with essential hypertension.

Response to Adrenocorticotrophic Hormone

Twenty units of adrenocorticotrophic hormone were administered every 6 hours over a period of 48 hours to five patients with essential hypertension. The daily excretion of urinary corticosteroids and aldosterone was determined (table 5) and plasma 17-hydroxycorticosteroids were measured at 0, 4, and 48 hours (fig. 5). Both groups included male and female patients. The responses were compared with those obtained in healthy subjects previously reported.[15] Although there were variations in response in the two groups, the mean values for both urinary 17-hydroxycorticosteroids and aldosterone were in the same range after the administration of adrenocorticotrophic hormone. The plasma levels of 17-hydroxycorticosteroids before and after adrenocorticotrophic hormone in both groups fell within the same range. These studies indicate that the adrenal glands of patients with essential hypertension are not more responsive to adrenocorticotrophin than those of normotensive individuals.

Steroid Content of Adrenal Glands of Patients with Malignant Hypertension

Adrenal glands from the two patients with malignant hypertension were analyzed for

Table 4

Excretion of 17-Hydroxycorticosteroids in Essential Hypertension

Cases	Sex	(yr.) Age	(mg./24 hr.) Range	(mg./24 hr.) Mean
Normotensive, not hospitalized	male	22-35	3.0-8.5	5.3
Normotensive, hospitalized	male	22-29	3.3-8.8	6.1
Essential hypertension, hospitalized	male	27-62	4.8-7.9	6.2
Normotensive, not hospitalized	female	20-50	2.0-6.0	3.5
Essential hypertension, hospitalized	female	44-63	2.9-6.8	4.2

Table 5

Response of Urinary Steroids to Adrenocorticotrophic Hormone

		17-Hydroxycorticosteroids mg./24 hr.				Aldosterone μg./24 hr.			
Cases	Number	Control	ACTH Day 1	ACTH Day 2	After ACTH		ACTH Day 1	ACTH Day 2	After ACTH
Normotensive	8	5.2	24.1	35.7	8.0	4.8	21.4	17.3	5.2
Essential hypertension	5	4.7	18.8	27.4	10.4	6.4	18.5	12.4	3.0

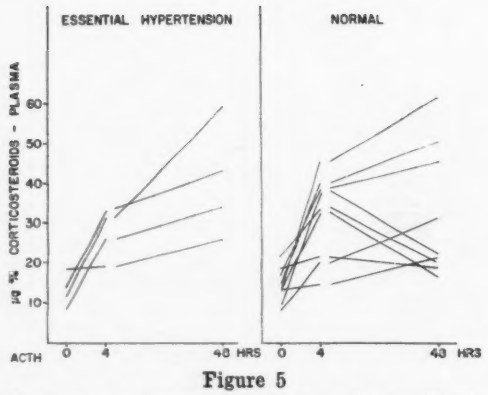

Figure 5

Response of plasma 17-hydroxycorticosteroids to adrenocorticotrophin in patients with essential hypertension and in normotensive individuals.

their content of adrenocortical steroids. At autopsy the glands were removed and frozen and later homogenized and extracted. The corticosteroids were separated by paper chromatographic procedures[14] and measured. The amount of the various steroids present in the tissue is expressed in micrograms of steroid per gram of adrenal tissue (table 1).

Although changes must have occurred in the steroid content between the time of death and freezing of the tissue, the high aldosterone content, 2.6 μg./Gm. in case 1 and 2.9 μg./Gm. of tissue in case 2, was increased many times above the values reported by Neher[16] in normal adrenal glands. The value for hydrocortisone was low in the first case and in the second case within the range given for the normal gland by Neher[16] and by Hudson and Lombardo.[17] Corticosterone was within the limits reported by these investigators.

Discussion

Although the majority of patients with benign essential hypertension, on a normal sodium intake, excreted amounts of aldosterone within the normal range, the mean value found in a group of 26 patients was significantly higher statistically than that observed in normotensive individuals. Whether this difference is of clinical significance in the etiology of the disease is not clear at the present time. Most of the patients were in an older age group than the normotensive individuals and little is known regarding the effect of age on aldosterone excretion. The excretion of other adrenal hormones, 17-hydroxycorticosteroids and 17-ketosteroids, declines with advancing years. If this same phenomenon occurs with aldosterone, then the difference between the two groups might be even greater. When renal disease was a secondary complication, the mean value was higher; when it was a primary factor, most of the values were above the normal range. Similar observations were observed in two patients with malignant hypertension on a normal sodium intake. These findings are essentially in agreement with those of Genest et al.[4–6] Laragh et al.[7] were unable to find any increase in the secretion rate of aldosterone in patients with benign essential hypertension; however, they did find significantly increased rates in patients with renal complications and in malignant hypertension.

Although the determination of the tetrahydro derivative does not appear to have the same accuracy as that for aldosterone, the mean value in a group of six patients with essential hypertension was considerably higher than that observed in normotensive individuals, 40 per cent of the values being above the highest value obtained in the normal group. The number of patients studied, however, was small compared to the number of normal individuals, and this ratio might change with an increasing number of assays. Very high amounts of the tetrahydro derivative were found in the urine of a patient with glomerulonephritis on a sodium intake of 100 mEq. per day.

Several possible explanations for the wide fluctuations in the urinary excretion of aldosterone that occur in some patients with hypertension can be suggested. These may reflect a variation in the secretion rate or an alteration in the metabolic degradation of aldosterone and its urinary excretion. If the former be so, then single determinations of an aldosterone secretion rate may not truly reflect the amount of aldosterone elaborated by the adrenal gland over a period of time,

and repeated parallel measurements would seem necessary until this matter is clarified. Fluctuations may also occur owing to emotional disturbance, and this certainly was a factor in a few cases. Similar increases have been observed in medical students during examinations when anxiety was present.[18] The possibility that the adrenal glands of patients with hypertension might be more responsive to adrenocorticotrophic hormone was considered. This did not appear to be the case, however, as both normotensive individuals and hypertensive patients showed comparable increases in urinary aldosterone as well as plasma and urinary 17-hydroxycorticosteroids following the administration of similar amounts of adrenocorticotrophic hormone. These observations do not exclude mediation by another humoral pathway.

Several studies with a variety of methods [19, 20] have failed to show an increase in the excretion of corticosteroids in essential hypertension, and in the present study the Porter-Silber corticosteroids were within the normal range. Fractionation of the individual steroids also failed to show any gross abnormality in the ratio of the different urinary corticosteroids.

The high amount of aldosterone found in the adrenal glands of the two patients with malignant hypertension suggests that these glands have been secreting excessive amounts of this hormone at the time of death. These amounts are higher than those reported by Neher[16] in tumors from patients with primary aldosteronism and only slightly lower than that observed by Genest[21] in a case of primary aldosteronism and adrenal hyperplasia. In this case the adrenal gland was removed surgically, and a content of 3.6 μg. aldosterone per gram of tissue was found.

These studies suggest that aldosterone may play some role in the etiology of essential hypertension but a direct causal relationship seems unlikely. The high excretion rates found in hypertensive patients with associated renal disease, whether of a primary or secondary type, would indicate a possible renal-adrenal interplay in this disease. The elevated values observed in malignant hypertension, with a subsequent fall on reversal of this syndrome, together with the increased concentration in the adrenal glands of patients examined post mortem, suggest that hypersecretion of aldosterone may play an important role in its pathogenesis.

Summary

Serial determinations of the urinary excretion of aldosterone have been made in hypertensive patients. Although the majority of patients with benign essential hypertension excrete amounts of aldosterone within the normal range, the mean excretion of 26 patients was significantly higher than that observed in normotensive individuals. When renal complications were present, the mean excretion was still further increased and in patients with malignant hypertension all the values were above the normal range.

The mean excretion of the tetrahydro metabolite of aldosterone was also found to be higher in patients with essential hypertension.

These patients have a normal response to adrenocorticotrophic hormone stimulation, urinary and plasma corticosteroids, as well as urinary aldosterone, showing comparable increases.

The aldosterone content of adrenal glands obtained post mortem from two patients with malignant hypertension was within the range observed by other investigators in primary aldosteronism.

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An Editor's Prayer to Contributors

Brevity in writing is the best insurance for its perusal.—VIRCHOW

Tomographic Evaluation of Hemodynamic Changes in Mitral Stenosis

With a Statistical Note on Normal Tomographic Findings

By M. J. DULFANO, M.D., AND H. ADLER, M.D.

THE LAST few years have witnessed a renewed interest in the roentgenologic interpretation of disturbances in pulmonary circulation. Because it is inexpensive and readily available, the plain chest x-ray has been mainly used.[1-10] It gives a good view of the major features but, by necessity, represents the superimposition of many structures and thereby limits the observations of details, especially in the hilar and lower parts of the lungs.[11-13]

Angiocardiography is undoubtedly the most adequate method for this study but it is expensive, time-consuming, and not without danger for the patient.[14, 15] Tomography utilizes the natural contrast between the blood-filled pulmonary blood vessels and the air-containing lung to good advantage.[16, 17] It constitutes an effective supplement to the use of plain chest x-ray in the assessment of mitral valvular disease.

The intention of our study is to demonstrate that routine tomography can give a very detailed estimation of the size, distribution, and contour of the pulmonary vessels; pathologic changes in the parenchyma, interstitial tissues, and pleura; and the configuration and size of some of the cardiac chambers. All these data can be correlated with the hemodynamic events in the lesser circulation.

Material and Methods

This study is based on 31 patients suffering from mitral valvular disease who were being evaluated for mitral commissurotomy. All except two were clinically diagnosed as having predominant or pure mitral stenosis. All of them underwent cardiac catheterization according to established technics.[18] The plain chest film and tomography were obtained within 3 weeks after catheterization. One hundred complete chest tomograms of individuals without evidence of heart disease served as controls.

Tomography was performed on a horizontal table with a focus-film distance of 140 cm., with use of a rotation angle of 45° and an exposure time of 0.8 second. The perspective enlargement factor ranges from 14.7 per cent in a layer of 8 cm. to 17 6 per cent in a layer of 11 cm.

Anteroposterior tomograms were routinely made at three levels, 1.5 cm. apart; the middle one was in the hilar region, this ordinarily means the layer 10 to 11 cm. in adults and 7 to 9 cm. in adolescents; one, 1.5 cm. dorsally, and one, 1.5 cm. ventrally from the hilar cut. Lateral tomograms usually required only two layers on each side; in normal adults the layers were 9 5 and 11 cm., and in adolescents 8 and 9 5 cm. from the lateral chest wall in the lateral decubitus position. When necessary, anterior oblique positions were added. The layers, the kilovoltage, and the milliamperes were adjusted to the body structure of the patients.

Normal Anteroposterior Tomograms*

In the hilar layer and around it a clear picture is usually given of the descending branch of the right pulmonary artery and the first branches leading to the three lobes. The width of the right descending branch, hereafter called hilar right pulmonary artery (numbered 1 in fig. 1), was easily measured at right angles to the bronchus and to the outer margin of the vessel. Its diameter ranged from 10.0 to 16 mm. The mean value ranged in the various age groups from 11.0 to 14.0 mm. These figures are in accordance with the results obtained by Schwedel and associates in plain chest films.[8]

The left main pulmonary artery (numbered 5 in fig. 1) was quite prominent in this position without overlapping other formations. Its width measured at a right angle to the left main bronchus

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*There are obvious limitations of measurement of vessels. These include defining the same point because of variations in branching, in size of patients, and in quality of film. Also the normal variations are wide. Nevertheless, the following findings in the normal provide a useful baseline for the assessment of the pathologic changes.

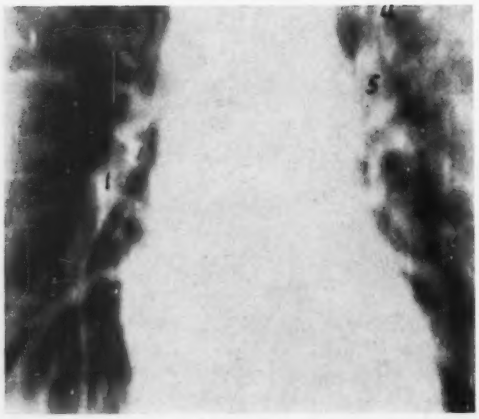

Figure 1

Normal anteroposterior tomogram: 1, hilar right pulmonary artery; 2, segmental arterial branch; 3, segmental vein of right lower lobe; 4, segmental vein of left upper lobe; 5, left main pulmonary artery.

ranged from 17 to 31 mm. Its mean values in the various age groups ranged from 20.2 to 25.8 mm. Medium-sized, segmental arteries (numbered 2 in figs. 1 and 3) both in the anteroposterior and lateral tomograms varied from 2.5 to 6.5 mm. in width. The mean values in the various age groups ranged from 3.5 to 4.7 mm. There were no significant differences in the size of the most peripheral vessels; they were usually 1 mm. wide.

The pulmonary veins were well visualized in the hilar layers, particularly in the lower part of the right hilus, where they cross the arteries (numbered 3 in fig. 1). The width of the segmental lower lobe veins ranged from 3.5 to 8 mm. The mean values in the various age groups ranged from 4.3 to 5.4 mm. Their point of entry into the left atrium was usually clearly outlined and marked its outer limit (fig. 4). The upper lobe veins run from the apex downward, parallel and externally to the arteries and are better seen on the hilar tomographic layers (numbered 4 in fig. 1). The width of the upper lobe veins ranged from 2.5 to 6 mm. The mean values in the various age groups ranged from 3.7 to 4.4 mm.

Normal Lateral Tomograms

In the right lateral view (fig. 2), the trunk of the right main pulmonary artery is seen end on. Its posterior border stands out, contrasting with the translucency of the stem bronchus, its inferior border contrasting with the lobar bronchus of the middle lobe. The anterior border is usually convex and clearly visible. The mean diameter of the round-like shadow was derived from the horizontal

Figure 2

Normal right lateral tomogram: 1, trunk of right pulmonary artery; 2, lobar inferior vein; 3, V_6 (lower lobe apical vein); 4, bulblike junction of right lung veins. Note the similar width of the segmental vessels in the upper and lower parts of the lung.

and vertical diameters. It ranged between 20 and 33 mm., and the mean value in the various age groups ranged between 21 and 28.8 mm.

In the left lateral view (fig. 3), the left main pulmonary artery is seen as a well circumscribed band that embraces the round translucency of the left main bronchus, runs dorsally to it and downward to the lower lobe. Its width ranged from 14 to 25 mm. The mean values in the various age groups ranged from 18 to 20.4 mm.

The segmental distribution of the pulmonary vessels is ordinarily recognized in both right and left lateral tomograms, thus giving a better insight into pathologic conditions of the vessels than routine anteroposterior tomography.

Lateral tomography is a valuable method for outlining size and distribution of the pulmonary veins. The inferior veins lie ventral to the arteries running parallel to them (figs. 3 and 7). The common basal venous trunk joins in the lower posterior part of the hilus with V_6, the vein of the apical lower lobe segment which runs in oblique direction downward and ventrally (fig. 2).[16] At entry into the left atrium, the veins are seen as a slight bulblike dilatation (fig. 6) which becomes

Figure 3

Mitral stenosis, early stage: 1, normal left main pulmonary artery; 2, segmental artery; 3, segmental vein, normal blood vessel and filling throughout; 4, slight displacement of left main bronchus.

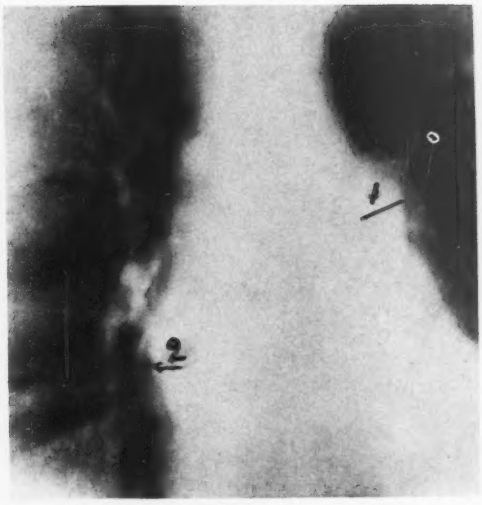

Figure 4

Mitral stenosis, early stage: normal width and vessel filling distribution throughout lung; 1, slight enlargement of left main pulmonary artery; 2, slight enlargement of left atrium.

progressively prominent with the advancing mitral stenosis (figs. 11 and 14). Topographically they seem to belong to the upper lobe venous system.

Encroachment of the anterior border of the heart shadow on the anterior thoracic wall is a valuable sign in cases of right ventricular hypertrophy. This sign is best visualized in the left lateral tomogram. Left ventricular hypertrophy is generally not so positively identified.

In the left lateral tomogram, left atrial enlargement can be indirectly disclosed by the narrowing and displacement of the left main bronchus, which is always clearly seen in this view (figs. 3, 11, and 13). The right anterior oblique tomogram is of great help in outlining the posterior margin of the enlarged left atrium by observation of the region of entry of the pulmonary veins.

Enlargement of the inferior vena cava may be delineated in the right lateral tomogram.

Intracardiac calcifications may be distinctly discerned in the left lateral tomograms.

Findings in Patients with Mitral Valve Disease

The analysis of our pathologic material centered around the following main details:

1. The size of the arteries at the level of the trunk of the right main pulmonary artery, the hilar right pulmonary artery, and the segmental branches. The degree of "tapering off" between the hilar and segmental branches was noted (table 1).[1, 3, 10]

2. The size of the common upper lobe veins, before their entry into the left atrium (table 1), and their segmental branches.

3. Parenchymal and vascular changes were integrated in three groups of signs: (a). The lung background (diminution of normal lung translucency. (b). The presence of A lines (seen as thin, curvilinear lines radiating to the hilar region,[19-21] B lines (horizontal lines running perpendicular to the costal pleura along the peripheral lobular septa. They are better seen in the plain film),[20, 22, 23] thickened fissure,[20] interlobar or free transudates.[12] (c). Changes in the blood vessel contour (tortuosity).[14] Each of these groups of signs was arbitrarily awarded a value of one unit. If all the signs were present (3a, b, c) and any was marked, allowance was made for one extra unit so that a limit of four units was set (table 1). It was our opinion that these signs (3a, b, c) represented evidence of impaired venous drainage and are so labeled in this paper (table 1).

4. The pattern of blood vessel filling throughout the lung, based essentially on Simon's work.[13] Four stages were adopted: (a). Normal distribution, i.e., equal throughout the lung. (b). Less filling in the lower lobes of the lung and increased filling in the whole of the upper lobes (including the apex of the lower lobe, which usually behaves functionally like the upper lobe. (c). Diminished filling in the lower lobes and increased filling only

Table 1

Individual Tomographic Correlation with the Hemodynamic Findings

Case no.	Clin. group	Drainage impairment units	Blood vessel filling pattern	Common ULV mm.	PCP mean mm. Hg	Arteries		Pulmonary arterial pressure mean mm. Hg	Pulmonary arterial resistance dynes sec cm^{-5}	Total pulmonary resis. dynes sec cm.$^{-5}$	Cardiac index L./mm./M.^{2}
						RPA (trunk)	"Taper off" mm.				
1	II	0	A	11	10	30	3	12	—	—	—
2	II	0	A	15	10	28	6	14	—	—	—
3	II	0	A	13	10	29	9	14	100	230	3.5
4	II	0	A	11	16	28	7	17	—	—	—
5	II	0	A	15	12	26	8	16	71	280	3.2
6	II	1	A	10	9	23	7	14	104	270	3.5
7	II-III	1	A	10	9	—	8	10	96	250	3.5
8	II-III	1	A	13	10	31	10	16	—	—	—
9	II-III	0	A	11	16	28	7	25	91	320	3.3
10	III	1	B	17	20	35	11	30	—	—	—
11	III	1	B	18	20	34	10	28	125	400	3.5
12	III	1	B	18	20	33	9	30	118	380	4.0
13	III	2	B	18	20	41	15	40	306	615	3.3
14	III	2	C	—	22	29	5	30	—	—	—
15	III	3	B	25	21	37	7	32	162	470	3.2
16	III	3	B	—	25	28	8	31	160	700	2.3
17	III	3	C	25	22	36	5	28	84	390	3.0
18	III	3	C	19	24	35	10	30	166	540	3.0
19	III	3	C	21	30	37	17	65	—	—	—
20	III	3	C	20	30	45	11	38	—	—	—
21	III	3	C	—	33	42	20	55	360	900	2.9
22	III-IV	3	B	24	24	39	13	45	230	450	3.0
23	IV	3	C	—	20	—	15	45	380	730	3.0
24*	IV	3	D	21	25	—	—	—	—	—	1.2
25*	IV	4	D	—	25	—	—	—	—	—	2.8
26	IV	3	D	26	35	39	15	50	106	850	2.4
27	IV	4	C	23	22	45	13	35	444	1100	1.5
28	IV	4	C	24	24	43	20	45	490	1050	2.1
29	IV	4	D	—	20	45	25	65	950	1430	2.5
30	IV	4	D	32	28	41	16	42	520	1750	1.2
31	IV	4	C	—	34	43	16	60	530	2000	2.0

Common ULV: Width of the upper lobe vein at the level of the left atrium. PCP: Mean pulmonary "capillary" pressure. Arteries, RPA: Trunk of right pulmonary artery diameter. "Taper off": Millimeter difference in width between hilar right pulmonary artery and segmental arteries.

*Pulmonary artery pressures and vascular resistances are not considered because of the "myocardial factor."

in some segments of the upper lobes. (d). Diminished filling throughout the lung without regional differences (table 1).

5. We took notice of several cardiac features: enlargement of the right ventricle and left atrium, calcifications, and shape of the heart in the left lateral tomogram.

Results

Venous Circulation

Drainage Impairment

Two units of drainage impairment marked the boundary between the milder and severer cases (table 1). Patients with less than two units belonged to clinical group II to early III (New York Heart Association Classification); their mean pulmonary "capillary" pressure was less than 20 mm., cardiac index above 3 L. per minute per M.^{2} and total pulmonary resistance below 400 dynes sec. cm.$^{-5}$.[18]

Increased signs of drainage impairment correlated well with increased disruption of the normal pattern of blood vessel filling in

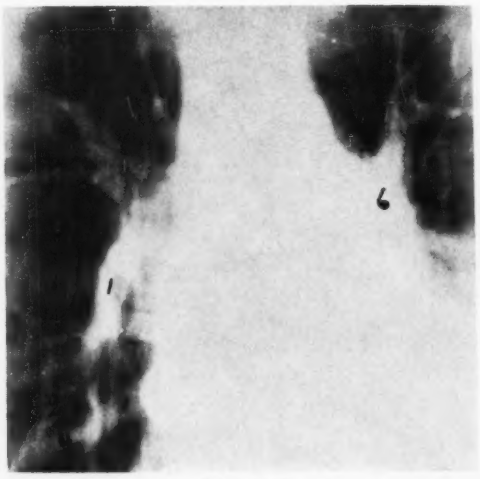

Figure 5

Mitral stenosis, early stage: 1, normal hilar and, 2, segmental branches of pulmonary artery; 3, normal right inferior vein with; 4, segmental branches. Note that the left uper segmental lobe vein, 5, is normal and of less width than the inferior segmental lobe veins.

the lung (table 1). The individual tomographic sign that correlated better with the degree of mitral impairment to flow (as expressed by the pulmonary "capillary" pressure) was the size of the common upper lobe vein as seen in the region of the left atrium in the right or left lateral tomograms. A common upper lobe vein less than 17 mm. in diameter meant pulmonary "capillary" pressure of less than 20 mm. Hg mean pressure (table 1).

Pattern of Blood Vessel Filling

Stage A was comprised of patients in clinical group II and early III whose pulmonary "capillary" pressure was less than 18 mm. Hg mean pressure, cardiac index more than 3 L. per minute per M.^{2}, and total pulmonary resistance of less than 300 dynes sec. cm.$^{-5}$. Stage D meant pulmonary "capillary" pressure usually above 25 mm., cardiac index less than 2.5 L. per minute per M.^{2}, and total pulmonary resistance more than 1000 dynes sec. cm.$^{-5}$. Stages B and C were intermediate (table 1). The results were in fair accordance with the analysis of signs of drainage impairment.

Figure 6

Mitral stenosis, early stage (right lateral tomogram): 1, the trunk of the right pulmonary artery is minimally enlarged, normal blood vessel filling distribution; 2, slightly enlarged right pulmonary veins at the level of the left atrium.

Arterial Circulation

The more dynamic behavior of the arterial circulation in mitral stenosis renders the roentgenologic correlation more difficult than on the venous side. The mean diameter of the trunk of the right pulmonary artery was measured in the right lateral tomograms. A diameter of 30 mm. was found in patients whose pulmonary artery systolic and mean pressure were in the region of 50 and 30 mm. Hg, respectively.

The correlation was better when we compared the millimeter difference in width of the hilar right pulmonary artery minus the segmental artery branches ("tapering off")

Table 2

Tomography and Hemodynamic Correlation

Case	Tomography: Venous: Drainage impairment units	Tomography: Venous: Common ULV	Tomography: Arterial: RPA mm.	Tomography: Arterial: "Tapering off" mm.	Hemodynamics: PCP mean mm. Hg	Hemodynamics: Pulmonary arterial pressure mean mm. Hg	Hemodynamics: Pulmonary arterial resistance dynes sec. cm.$^{-5}$	Hemodynamics: Total pulmonary resistance dynes sec. cm.$^{-5}$	Hemodynamics: Cardiac index L./min./M.^{2}
1 to 12	Early Stage: clinical group II, early III, blood filling pattern A-B								
Mean	0-1	13.5	29.6	7.7	13.4	18.8	101	318	3.5
Range		10-18	23-35	3-11	6-20	10-30	71-125	230-400	3.2-4.0
13 to 23	Intermediate Stage: clinical group III, blood filling pattern B-C								
Mean	2-3	21.8	36.9	14.6	24	40	193	600	3.0
Range		18-25	28-45	5-20	18-30	28-65	84-380	390-900	2.3-3.3
24 to 31	Advanced Stage: clinical group IV, blood filling pattern C-D								
Mean	3-4	25	42.6	17.5	27.2	50	507	1350	2.0
Range		21-32	39-45	13-25	22-35	35-65	106-950	850-2000	1.2-2.8

See table 1 for key to abbreviations.

in the anteroposterior tomogram (table 1). The boundary between milder and severer cases was at the width difference of 10 mm. When this difference was below 10 mm., the pulmonary artery systolic pressure was less than 50 mm. Hg, the mean pressure was less than 30 mm. Hg, and the pulmonary arteriolar resistance was less than 200 dynes sec. cm.$^{-5}$ (table 1).

Tomographic-Hemodynamic Correlation

A clear picture of tomographic-hemodynamic correlation could not be obtained by the use of individual tomographic signs. The integration of several tomographic signs, however, allowed us to define the progression of the hemodynamic derangement and to classify them into 3 stages: early, intermediate, and advanced (table 2).

Early Stage. Minimal signs of impaired venous drainage (0 to 1) unit, normal pattern or minimal disturbance of the blood filling pattern (stages A-B), minimal stasis of common upper lobe vein (mean 13.5 mm.), slight engorgement of the trunk of the main right pulmonary artery (in right lateral tomogram —mean 29.6 mm.), and slight increase in the degree of "tapering off" (in the anteroposterior tomogram, the width difference between the hilar right pulmonary artery minus the segmental branches had a mean value of 7.7 mm.) (figs. 4-7).

These patients belonged to clinical group II and early III. Their mean pulmonary "capillary" pressure and pulmonary artery pressure were 13.4 and 18.8 mm. Hg, respectively. Their mean pulmonary arteriolar resistance and total pulmonary resistance was 101 and 318 dynes sec. cm.$^{-5}$, respectively. The cardiac index remained normal with a mean value of 3.5 L. per minute per M.^{2}.

Intermediate Stage. Impaired venous drainage of 2 to 3 units, abnormal pattern of blood filling (stages B-C), increased stasis of the common upper lobe vein (mean 21.8 mm.), and greater engorgement of the trunk of the right pulmonary artery (mean 36.9 mm.). The mean degree of arterial "tapering off" in the anteroposterior view was 14.6 mm. (figs. 8-11).

All the patients belonged to clinical group III. Their mean pulmonary "capillary" pressure and pulmonary artery pressure was increased to 24 and 40 mm. Hg, respectively. Their mean pulmonary arteriolar resistance and total pulmonary resistance were 193 and 600 dynes sec. cm.$^{-5}$, respectively. The cardiac index decreased to the lower limits of normal and had a mean value of 3.0 L. per minute per M.^{2}.

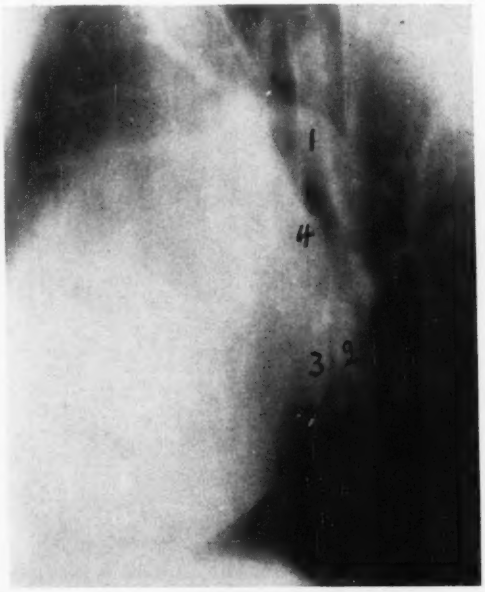

Figure 7

Mitral stenosis, early stage (left lateral tomogram): 1, slightly enlarged left main pulmonary artery; 2, segmental artery; 3, segmental vein, the distribution of the blood vessel filling is normal; 4, slight displacement of the left bronchus. Note the piriform shape of the heart.

Advanced Stage. Maximal signs of impaired venous drainage (3 to 4 units) and disruption of the blood filling pattern (stages C-D). All the patients had B or A lines, marked tortuosity of the blood vessels, the filling was poor throughout the lung, interlobar and free transudates were prominent. The common upper lobe vein and trunk of right pulmonary artery were maximally dilated (mean 25 and 42.6 mm., respectively). At this stage, artery size may be misleading if the right ventricular muscle is functionally inefficient. In such cases, observation of the venous circulation will still show the true advanced stage of the disease (figs. 12-14).

In this stage all the patients belonged to clinical group IV. Their mean pulmonary "capillary" pressure and pulmonary artery pressures were 27.2 and 50 mm. Hg, respectively. Their mean pulmonary arteriolar resistance and total pulmonary resistance were extremely elevated to the level of 507 and 1350 dynes sec. cm.$^{-5}$, respectively. The cardiac index was always below normal with a mean value of 2.0 L. per minute per M.^{2}.

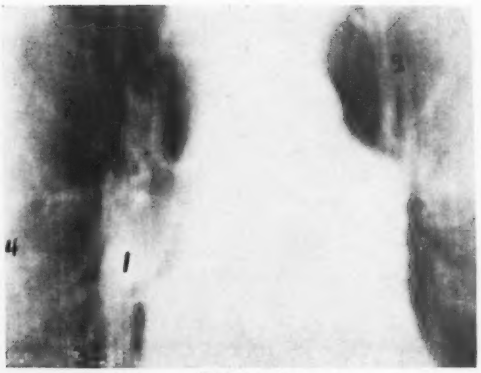

Figure 8

Intermediate stage: 1, marked dilatation of hilar right pulmonary artery, 2, the upper lobe vessels are wider than the lower lung vessels; 3, the vessels show tortuosity and their contour is blurred; 4, marked septal lines in right lower zones. Note the ground glass opacity of the background.

Heart Shape. As an incidental observation, we noticed in the left lateral tomogram that the heart shape exhibited a feature characteristic of cases of *pure* mitral stenosis. It resembled a pear standing on its narrower pole. This shape is apparently caused by the dilatation of the upper parts of the heart (the right ventricle and left atrium) without a corresponding dilatation of the lower half, particularly of the left ventricle (fig. 7). It may also be related to the usual clockwise rotation of the heart in mitral stenosis. The patients who also had an enlarged left ventricle due to added mitral insufficiency or aortic valve disease did not develop this shape.

Discussion

The pulmonary circulation is a most sensitive indicator of the hemodynamic derangement caused by mitral valvular disease. This can best be ascertained by studying the appearance of the pulmonary veins and the arteries separately. Throughout the course of the disease, the veins respond to changes in pressure by active constriction in the lower lobe and initial compensatory dilatation in the

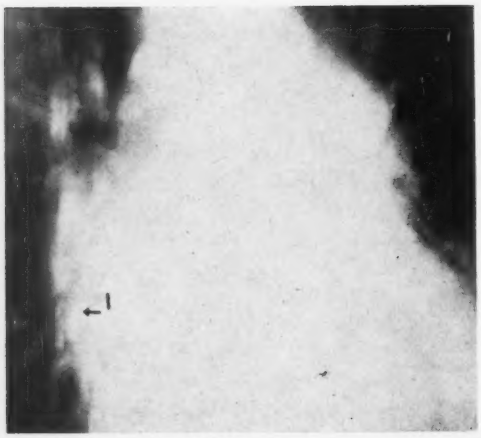

Figure 9

Intermediate stage: 1, marked left atrium enlargement; 2, marked "tapering off" of arteries and veins in the lower lobe segments and enlargement of upper lobe vessels.

upper lobes as described by Simon.[15] Later this condition is maintained by organic changes. The arteries bear this increased pressure in two fashions: at the beginning, the pressure increase is equivalent to that in the vein in order to keep the same pressure gradient for ensuring forward flow; above the critical level of 25 mm. Hg the pulmonary artery pressure rises in a disproportionate amount to the venous pressure.[24]

Thus, venous pressure becomes a variable dependent on two factors: the degree of stenosis of the mitral valve and the amount of blood flow passing through the barrier of arteriolar resistance. On the other hand, pulmonary artery pressure and size fluctuate according to the pulmonary arteriolar resistance and the effectiveness of the right ventricular muscular pump.

These many variables, which can only be ascertained by cardiac catheterization, account for some of the failures of roentgenologic estimation of the hemodynamics in mitral stenosis, primarily because most of the attention has been given to the arterial tree.[2, 5, 6, 8, 10, 21, 25] Therefore, we tried to correlate all the roentgenologic signs with the hemodynamic findings and, after giving them

Figure 10

Intermediate stage (right lateral tomogram): 1, enlarged trunk of right pulmonary artery. Note the better filling of blood vessels in the upper part of the lung.

numerical value, tried to obtain a total picture. In this analysis, the greatest attention was given to the pulmonary veins and their drainage. This drainage in mitral stenosis is effected in several ways: (1) through the pulmonary veins; (2) by lymphatics; (3) by pulmonary-bronchial venous anastomosis.[26, 27]

The first way can be followed quite well tomographically by measuring the size of the veins in their confluence into the left atria, especially in the lateral tomograms (figs. 6, 11, and 14).

The second way was appraised by the presence of A and B lines and by the presence of thickened fissures, intralobar transudates, and free transudates in the costophrenic angles, which we believe are different expressions of the same hemodynamic phenomenon (figs. 8 and 12).[20, 23] The third way cannot be asserted roentgenologically.

Tomography is a very helpful method in differentiating true parenchymal nodules from

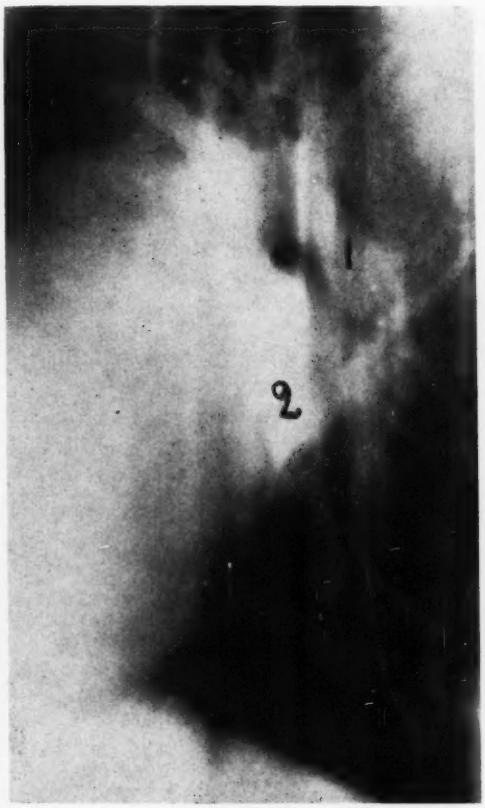

Figure 11

Intermediate stage (left lateral tomogram): 1, slight enlargement of left main pulmonary artery; 2, bulblike enlargement of the left pulmonary vein. Reduced blood vessel filling in the lower parts of the lung and increased in the upper lobe, especially in the anterior segment.

sections of blood vessels that have become tortuous; their pathway is ill defined and in a plain chest film, due to superimposition of many layers, they may be confused with nodules. We repeatedly found this feature of tortuous vessels in the more severe cases of mitral stenosis, confirming early angiographic observations (figs. 12 and 14).[14] The survey of our plain films did not allow us to make this differentiation clearly in every case.

The physiologic analysis of the pulmonary drainage, when considered from all aspects, brought us to coin the phrase *"impaired venous drainage,"* which is an expression not

Figure 12

Advanced stage (right lateral tomogram): note the marked blurring of the contour of the blood vessels and their tortuous course; 1, very thick interlobar fissure.

only of narrowing of the mitral valve, but also of its effects upon the pulmonary parenchyma. Impaired venous drainage proved to be a much better index than the currently used correlations of left atrial pressure with individual roentgenologic signs and represents a better expression of so-called degree of venous congestion.[24]

Another approach to the hemodynamic effects of mitral disease is the study of the pattern of the filling of blood vessels throughout the lung. Simon gave a most lucid interpretation of this pattern with special reference to the veins, but because of the limitations of the chest x-ray, he was only able to grade the changes in the upper lobes though his observations embraced all the vessels.[13] Our study confirms his results but we were able to go further, since tomography permitted us

Figure 13

Advanced stage (left lateral tomogram): the peripheral blood vessels are all small, tortuous, and blurred; great enlargement of the left main pulmonary artery; note extreme displacement and narrowing of the left bronchus, 1, between the enlarged left main pulmonary artery and left atrium.

Figure 14

Advanced stage (right lateral tomogram): 1, extreme enlargement of the trunk of the right pulmonary artery and, 2, right veins; both are very blurred. Note marked tortuosity and thinning of blood vessels and ground glass opacity of the pulmonary background.

to visualize the veins in all the lobes of the lung more clearly. The following facts were seen in regard to the medium-sized veins: (a). In the very mild cases, the lower lobe veins, as in normal individuals, may still be larger than the veins in the upper lobe (figs. 1 and 5). (b). With advance of the mitral obstruction, there appears the "shunting away" of blood toward the upper lobe veins, which become engorged (figs. 8, 9, and 10). This phenomenon, at a relatively early stage, was considered by Simon to be due to early vasoconstriction of lower lobe arteries, resulting from the higher hydrostatic pressure in the lower lobes in the standing position.[13] This finding in the *lying position* of the tomographic technic, confirmed that *organic* changes in the lower lobe arteries and veins become superimposed on the vasoconstriction fairly early.[13] (c). In the advanced stages, this upper lobe engorgement does not recede "in toto." Usually, the anterior segments are the last to maintain it (fig. 11). (d). The veins of the apex of the lower lobe (V_6) behave functionally like the upper lobe veins. (e). *Within* lung segments, the arteries and veins appeared generally to be of the same caliber (figs. 10 and 11).

The measurement of the size of the arteries alone proved to be much less contributory to the assessment of the severity of mitral disease. Absolute values of pressure and resistance were correlated only within broad limits with the roentgenologic findings and our results were in general agreement with previous observations.[1, 8, 10, 14, 21] Lack of correlation between pulmonary artery size and pulmonary artery pressure, especially in severe cases, may be due not only to intrinsic alterations in vessel walls, according to Lukas,[28] but also to failure of the right ventricular myocardium to keep pace with increased resistances[29] (cases 24 and 25, table 1). We

never saw a patient with severe pulmonary artery hypertension who had a hilar pulmonary artery of normal size.

The assessment of the degree of arterial "tapering off" still remains the most useful correlation with arterial pressure. For this purpose, tomography is considerably superior to plain chest x-ray. It was brought out that the vascular resistance, as expressed by the sudden narrowing of the arteries is effected in the medium-size arteries and not in the smaller ones. This observation would be in favor of an active muscular mechanism, since the muscular coat is better developed in the bigger than in the smaller arteries. The study of the most peripheral branches proved to be of no value in mitral stenosis.

The progressive slowing of the pulmonary circulation with the advance of the disease can only be seen by angiography.[14] Nonetheless, there is a parallel tomographic sign, especially in the right lateral position. In this view, an idea of this retardation of flow can be obtained by the progressive increase in size of both the right main pulmonary artery and the confluence of the upper lobe veins into the left atrium (figs. 11 and 14).

Summary

The hemodynamic findings in 31 patients with mitral valvular disease were correlated with the signs obtained by chest tomography. The normal and pathologic findings are described. The advantages of the tomographic technic for the study of the pulmonary vasculature are pointed out.

The progression of mitral valve narrowing was considered to be best related to the integrated picture of "impaired venous drainage." On this basis, three stages were defined.

The over-all response of the pulmonary circulation to the severity of the disease can be judged by the pattern of blood vessels filling throughout the lung.

It is concluded that for the evaluation of mitral valvular disease routine tomographic technic can indicate many of the essential hemodynamic findings with less hazard than either angiography or cardiac catheterization.

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Men that look no farther than their outsides, think health an appurtenance unto life, and quarrel with their constitutions for being sick; but I, that have examined the parts of man, and know upon what tender filaments that Fabrick hangs, do wonder that we are not always so; and, considering the thousand doors that lead to death, do thank my God that we can die but once.—Sir Thomas Browne. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1960, p. 69.

A Hemodynamic Technic for the Detection of Hypertrophic Subaortic Stenosis

By EDWIN C. BROCKENBROUGH, M.D., EUGENE BRAUNWALD, M.D., AND ANDREW G. MORROW, M.D.

IT IS NOW well appreciated that following a successful valvulotomy for valvular pulmonic stenosis, muscular hypertrophy in the right ventricular outflow tract may persist and be responsible for a significant resistance to right ventricular ejection.[1-3] Similar muscular obstruction to the left ventricular outflow has also been noted in patients following surgical relief of discrete valvular or subvalvular stenosis. Obstruction to left ventricular ejection resulting from contraction of hypertrophied muscle in the left ventricular outflow tract, without antecedent aortic valvular or subvalvular stenosis, has recently been recognized as a distinct disease entity.[4-10] Although a variety of names have been attached to this malformation, "idiopathic hypertrophic subaortic stenosis" has appeared to us to be most appropriate and the clinical, hemodynamic, and angiographic features in 14 patients studied at the National Heart Institute have been detailed elsewhere.[10]

In contrast to the usual forms of obstruction to left ventricular ejection in which the orifice size is fixed, in hypertrophic subaortic stenosis the obstruction in the outflow tract relaxes during diastole and narrows during ventricular systole.[10] This obstruction to left ventricular outflow results from myocardial contraction and it might be anticipated that alterations in the force of contraction could modify the effective orifice size of the left ventricular outflow tract. Accordingly, it was reasoned that the more forceful ventricular contraction which accompanies the compensatory beat following a premature contraction might narrow the orifice, reduce the stroke volume and, therefore, the systemic arterial pulse pressure. In contrast, in patients with the discrete forms of obstruction to left ventricular outflow, the increased force of contraction following the compensatory pause after a premature beat is accompanied by an increase in the systemic pulse pressure. This report consists of an analysis of left ventricular pressure pulses, which was undertaken in order to throw further light on the mechanism of the obstruction to left ventricular ejection in patients with hypertrophic subaortic stenosis, as well as to search for a simple method that might be useful in identifying patients with this lesion.

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Material and Methods

The catheterization data from 87 patients with aortic stenosis, studied during the last 18 months, were reviewed. Eleven patients had idiopathic hypertrophic subaortic stenosis and one patient secondary hypertrophic subaortic stenosis, these diagnoses having been established by selective left ventricular angiocardiography or at operation.[10] Forty-five patients had acquired aortic valvular stenosis and 30 patients had congenital aortic stenosis of the valvular, discrete subvalvular, or supravalvular type. The diagnosis was proved at operation in all 75 patients in the latter two groups.

Left ventricular pressure measurements were obtained by the transseptal,[11] transbronchial,[12] and anterior percutaneous[13] technics or by direct needle puncture at operation. Simultaneous left ventricular and arterial pressure tracings were analyzed and values for the peak left ventricular systolic pressure, the systemic arterial pulse pressure, and the duration of diastole were determined. The last was considered to be the time interval between the dicrotic notch and the upstroke of the subsequent beat. The average values obtained from three beats that did not follow a premature contraction were compared with the average values from three beats, each of which was the first normally conducted beat to follow the compensatory pause after a premature contraction. In two patients with idiopathic hypertrophic subaortic stenosis only a single premature ventricular contraction was available for analysis.

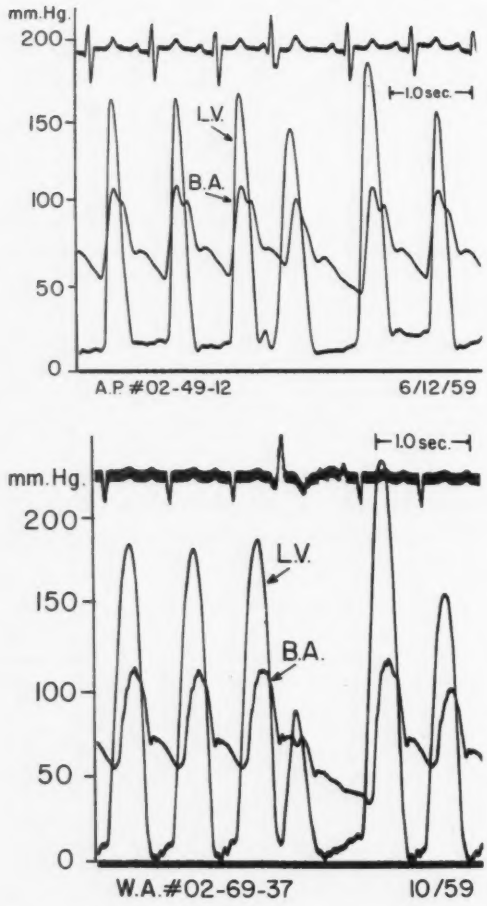

Figure 1

Simultaneous left ventricular and brachial artery pressure tracings, in a patient with acquired valvular aortic stenosis (A) and a patient with congenital, discrete subvalvular stenosis (B). An increase in the arterial pulse pressure accompanies the rise in peak left ventricular systolic pressure following the premature contractions.

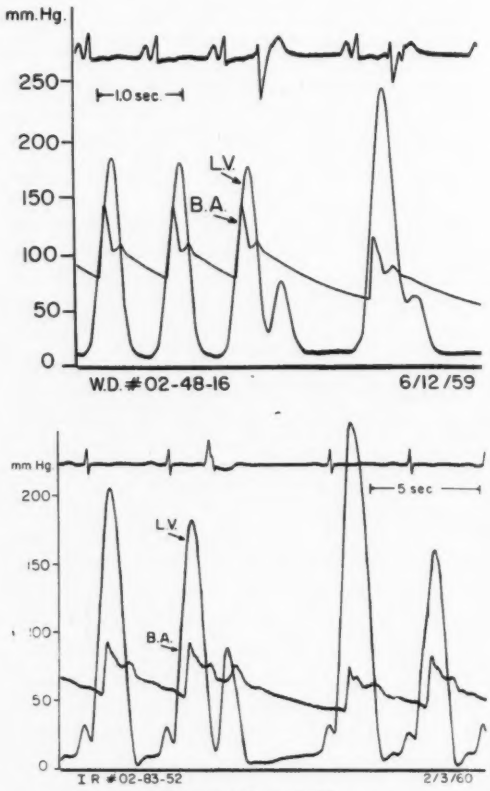

Figure 2A and 2B

Simultaneous left ventricular (LV) and brachial artery (BA) pressure tracings in two patients with hypertrophic subaortic stenosis. Following a premature ventricular contraction, the arterial pulse pressure narrows in association with an increased left ventricular systolic pressure.

Results

In all patients, the first normally conducted beat following the compensatory pause after a premature contraction was characterized by an elevation of the left ventricular systolic pressure. This increased left ventricular pressure was accompanied by a widened arterial pulse pressure in the patients with valvular and discrete subvalvular stenosis (fig. 1A, 1B). The opposite occurred, however, in the patients with idiopathic hypertrophic subaortic stenosis; the pulse pressure narrowed, in spite of a significant increase in left ventricular systolic pressure (fig. 2A, 2B). This paradoxical response of the arterial pulse pressure was characteristic of all but one of the patients with hypertrophic subaortic stenosis; in this patient only one premature ventricular contraction was recorded and the pulse pressure of the post extrasystolic beat was identical to the pulse pressure of the control beats. Figure 3 illustrates the relationship between the left ventricular systolic pressure

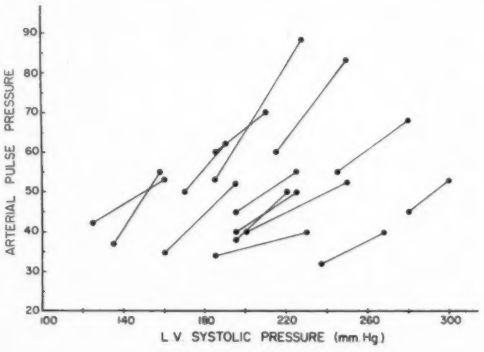

Figure 3

The relationship between the peak left ventricular systolic pressure and the arterial pulse pressure in normal beats, in comparison with those beats that followed a premature ventricular contraction, in 15 patients representative of the group with the discrete forms of aortic stenosis. In each instance the point on the left represents this relationship during normally conducted beats and the point on the right represents this relationship following ventricular premature contractions in the same patient.

and the arterial pulse pressures in normal beats as well as in those that followed premature ventricular contractions in 15 patients with the discrete forms of aortic stenosis. The results in these patients are representative of those obtained from the entire group. In a similar manner the relationship between the duration of diastole and the pulse pressure in these patients is shown in figure 4. In each instance the arterial pulse pressure varied directly with the left ventricular systolic pressure and with the duration of diastole.

Figure 5 illustrates the relationship between the left ventricular systolic pressure and the arterial pulse pressure in eight patients with hypertrophic subaortic stenosis. The relationship between the duration of diastole and the pulse pressure in these patients is shown in figure 6. The arterial pulse pressure varied inversely with the left ventricular systolic pressure and with the duration of diastole in any given patient. In the other three patients with hypertrophic subaortic stenosis the results were identical to those plotted in figures 5 and 6.

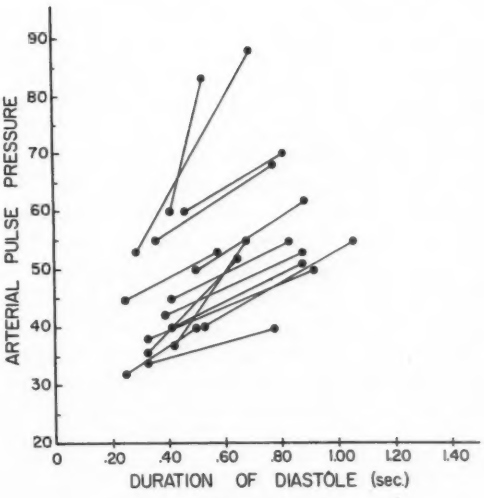

Figure 4

The relationship between the duration of diastole and the arterial pulse pressure for the same beats that are analyzed in figure 3.

Discussion

Certain clinical and hemodynamic features have been useful in suggesting the diagnosis of hypertrophic subaortic stenosis.[10] In contrast to the findings in patients with valvular or discrete subvalvular aortic stenosis, the murmur in these patients is most prominent along the left sternal border or at the apex. Either no thrill, or only a faint one, is present over the base of the heart and along the carotid vessels, and on roentgenographic examination there is no post-stenotic dilatation of the aorta. The arterial pulse is brisk to palpation and recordings of the arterial pressure pulses generally show a rapid upstroke in early systole, followed by a sudden decline in midsystole. While these signs may be helpful in suggesting the diagnosis, they are not specific, and the definitive preoperative diagnosis is based on the localization of the obstruction to the outflow tract of the left ventricle and the demonstration that the outflow tract narrows only during ventricular systole. In general, retrograde catheterization of the left ventricle from the aorta and selective left ventricular angiocardiography have therefore been necessary. In view of the appreciable

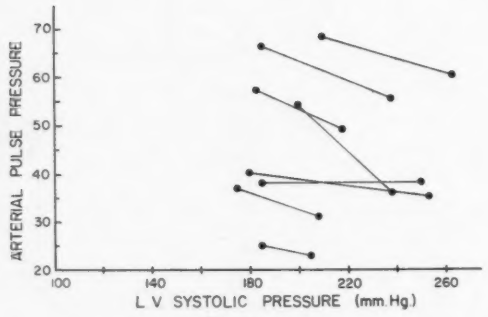

Figure 5

The same relationship as that depicted in figure 3, in eight patients with idiopathic hypertrophic subaortic stenosis.

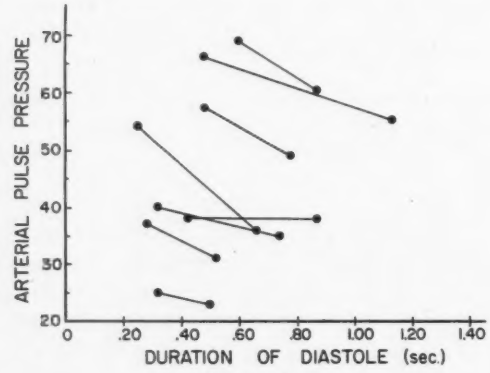

Figure 6

The same relationship as that depicted in figure 4, in eight patients with idiopathic hypertrophic subaortic stenosis.

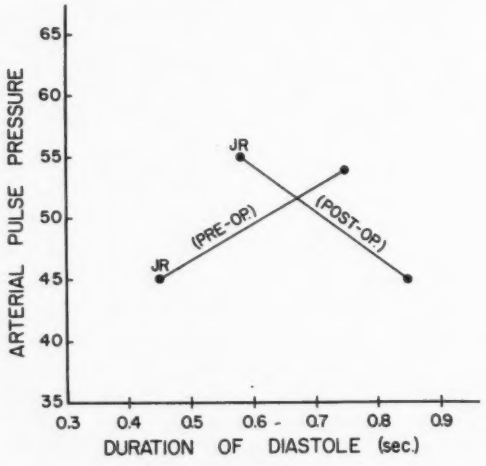

Figure 7

Comparison of preoperative and postoperative pulse pressure analyses in a patient with hypertrophic subaortic stenosis secondary to a discrete subvalvular obstruction.

risk, discomfort, and expense associated with these procedures, the need for a simple, reliable diagnostic test is clear.

The longer filling period following a premature ventricular contraction results in a greater left ventricular end-diastolic volume and, in accordance with the Frank-Starling mechanism, a greater force of ventricular contraction. The difference in the arterial pressure pulse produced by this increased contractile force has permitted separation of patients with hypertrophic subaortic stenosis from those with fixed obstruction to left ventricular ejection. In patients with valvular or discrete subvalvular stenosis, the stroke volume, and therefore the arterial pulse pressure, increases along with the force of left ventricular contraction. In the absence of aortic stenosis or in the presence of only moderate obstruction, changes in the arterial systolic and pulse pressures generally reflect similar changes in left ventricular systolic pressure. As observed by Breall and Shaffer,[14] however, in patients with *severe* aortic stenosis the peak arterial pressure remains relatively constant in spite of variations in left ventricular pressure. Even in such patients a longer diastolic filling period is associated with a lower diastolic pressure and a wider pulse pressure in the subsequent beat. In contrast, in patients with hypertrophic subaortic stenosis, the longer filling period following a premature ventricular contraction is followed by a smaller pulse pressure. This paradoxical decrease in pulse pressure is probably an expression of a reduction in orifice size. Since in these patients the obstruction is produced by contraction of hypertrophied muscle, it would not be surprising if the severity of the obstruction were a function of the strength of contraction. Thus, in addition to the angiocardiographic evidence for striking variation in the diameter of the outflow tract during

various phases of the cardiac cycle, these pulse pressure changes suggest that beat-to-beat variations in the size of the outflow tract also occur.

One patient with secondary muscular hypertrophy of the left ventricular outflow tract was studied. This 16-year-old boy had a systolic pressure gradient of 120 mm. Hg across an area of discrete subvalvular stenosis. Three weeks after an operation in which a thin subaortic membrane was completely resected, a gradient of 70 mm. Hg persisted. This residual gradient had completely disappeared when he was again catheterized 18 months later, confirming the impression that it had been caused by secondary muscular hypertrophy.[6] Analysis of his pressure pulses demonstrated that preoperatively his responses were typical of those seen in patients with "fixed" stenosis, while immediately after operation the parodoxical response characteristic of hypertrophic subaortic stenosis was present (fig. 7). It seems likely that before operation in this patient the stenotic subvalvular membrane prevented hemodynamic expression of the obstruction produced by the muscular hypertrophy. After operation, however, the persistence of muscular hypertrophy in the outflow tract resulted in dynamics identical to those observed in patients with idiopathic hypertrophic subaortic stenosis.

It is an interesting paradox that the Frank-Starling mechanism, which usually serves to increase the stroke volume when there is greater diastolic filling, appears to increase the stenosis and actually diminishes the stroke volume in patients with hypertrophic subaortic stenosis. It is possible that sustaining this stronger force of contraction for more than a few beats may be deleterious and that inotropic drugs should be used with caution in these patients.

The ultimate clinical usefulness of the hemodynamic sign described for differentiating systolic from fixed aortic stenosis will depend upon its specificity, but also, before it can be applied, pressures must be recorded after several extrasystolic beats. These were recorded in all but one patient with hypertrophic subaortic stenosis in whom simultaneous left ventricular and arterial pressures were available for analysis. If a deliberate attempt were made to record pressures during the occurrence of extrasystoles, their frequency in the course of left heart catheterization would permit the hemdoynamic analysis described above to be made in almost every patient undergoing this procedure.

The observation that the pulse pressure varies inversely not only with the peak left ventricular systolic pressure but also with the duration of the preceding diastole makes it possible to distinguish hypertrophic subaortic stenosis from the discrete forms of obstruction to left ventricular outflow when only an arterial pressure pulse is available. Such recordings may be obtained during right heart catheterization, when premature ventricular contractions are frequently induced. In the presence of spontaneously occurring premature contractions, it would be possible to distinguish the two forms of obstruction by inspection of direct or indirect arterial pressure tracings obtained without simultaneous intracardiac pressures and perhaps by careful palpation of the peripheral pulse.

Summary

In the presence of valvular aortic stenosis or of discrete subvalvular stenosis, the narrowed orifice is constant and its size is not altered by changes in the force of ventricular contraction. In hypertrophic subaortic stenosis the orifice narrows during systolic contraction of the hypertrophied muscle in the left ventricular outflow tract and the orifice size therefore is a function of the force of left ventricular contraction. In 75 patients, proved to have the discrete, "fixed" type of aortic or subaortic stenosis the beats following the compensatory pause after a premature contraction were always characterized by higher left ventricular systolic pressures and larger systemic arterial pulse pressures than the normal beats, i.e., arterial pulse pressure varied directly with left ventricular systolic pressure and with the duration of diastole. In 12 patients proved to have hypertrophic subaortic stenosis, the beats following premature

contractions always exhibited *lower* arterial pulse pressures than did the normal beats, i.e., arterial pulse pressure varied *inversely* with left ventricular systolic pressure and with the duration of diastole. The distinction between these two types of obstruction to left ventricular outflow may be established with confidence by this analysis of the effects of premature ventricular contractions on either the simultaneously recorded left ventricular and arterial pressure pulses, or on the arterial pressure pulses alone. The recognition of hypertrophic subaortic stenosis is essential in formulating a rational plan of treatment for all patients with obstruction to left ventricular outflow, and the hemodynamic technic described affords a simple but reliable diagnostic approach.

Addendum

Since figures 5 and 6 were prepared for publication we have studied three additional patients with idiopathic hypertrophic subaortic stenosis. In each instance the arterial pulse pressure varied inversely with left ventricular systolic pressure and with the duration of diastole.

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Ballistocardiographic Study in Severe Anemia

By O. P. TANDON, M.D., AND B. C. KATIYAR, M.D.

ANEMIA affects the heart by impairing the oxygen supply of the myocardium and by increasing the mechanical load on the heart through alterations in the circulatory dynamics. Irrespective of the cause of anemia, the cardiac and circulatory disturbances are identical as long as the anemia is severe. With the introduction of ballistocardiographic technics, a new tool became available for the study of the force of cardiac contractions in various disease states; this technic, however, has not been adequately exploited to investigate the cardiac changes in anemia. Dock and his colleagues[1] made only casual references to the ballistocardiographic changes in anemia, stating that the tracings showed high-amplitude waves indicating increased force of cardiac contraction. They noted that the correction of anemia caused a reversion of the high-amplitude waves toward normal. In a study of severely anemic patients, Sanghvi and Banerjee[2] noted abnormal tracings in every case, the abnormalities consisting of tall or bifid H; fused HJ; broad or bifid J; short, absent, or notched K; tall L, M, or N; and totally bizarre complexes of low amplitude. In a third of their cases, large systolic complexes were seen, and the pattern was grossly abnormal in few of these. In significant contrast to the high-amplitude waves, totally bizarre complexes of small amplitude and grade-IV abnormality were seen in the minority of cases. These authors noted that, in the vast majority of cases, ballistocardiographic abnormalities persisted even after the cure of anemia and that the degree of abnormality often remained unaltered by the correction of anemia. In order further to document the ballistocardiographic changes, a study of 10 cases of severe anemia is reported.

Material and Methods

The present study consists of 10 cases of severe anemia due to hookworm infestation. The age, sex, weight, and hemoglobin levels (before and after the treatment) are given in table 1.

The presence of any clinically detectable heart disease was excluded. The study was carried out by Dock's direct body ballistocardiograph with the electromagnetic pick-up. Hospital beds being unstable and therefore unsuited for ballistocardiographic study, a rigid hard wooden board was used during the recording of the ballistocardiogram. A double-channel electrocardiographic machine was used to record the tracings. On channel A of the machine, the ballistocardiogram was taken while channel B was used to record the lead II of the electrocardiogram. The tracings were recorded in the recumbent position with the breath held in normal respiration, in deep inspiration (with the mouth open to avoid Valsalva effect), and again in deep expiration. The instrument was standardized so that a deflection of 10 mm. was obtained with a current of 1 mv. In each case, the ballistocardiographic pattern was studied before and after the treatment.

As a control, 20 healthy normal subjects were studied. The tracings of these normal individuals (fig. 1) were used to determine the maximum normal range of height and duration of individual waves. The waves outside this range were regarded as abnormal. On the basis of this control series the various waves have, in subsequent results, been designated as small, tall, deep, or wide. The criteria for these designations are given in table 2. The records were graded as I, II, III, and IV based on the criteria of Brown et al.[3, 4]

Results

All the tracings on admission showed ballistocardiographic abnormalities (table 3 and figs. 2-6). Detailed changes are sufficiently evident by inspection of the tables and figures and therefore are not described here.

The ballistocardiographic abnormalities can be summarized as follows: 1. Before treatment, most of the waves were smaller than normal. They showed a tendency to regain their normal size after treatment. 2. In few tracings, the waves were taller than normal after treatment (figs. 3 and 4) but never before treatment (except in 2 cases where J wave was tall even on admission). 3. There were tracings where waves remained smaller in size even after treatment. It was possible

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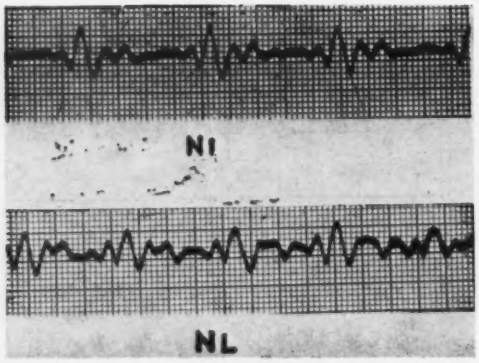

Figure 1

Ni and Nl are tracings from 2 clinically normal subjects.

Table 1

Clinical Data in Ten Cases of Anemia

Case no.	Age	Sex	Weight in pounds	Hemoglobin in grams per cent: Before treatment	Hemoglobin in grams per cent: After treatment
1	50	M	130	4.0	8.6
2	30	M	122	2.6	9.5
3	24	F	105	5.2	10.0
4	25	M	110	3.5	7.5
5	28	M	118	3.0	8.4
6	30	F	98	5.8	9.4
7	35	F	108	3.0	9.0
8	28	F	114	3.0	9.0
9	24	M	104	4.0	8.5
10	19	F	85	6.0	11.0

that they might have attained their normal size by the time the hemoglobin had reached normal. Actually all cases were discharged before normal hemoglobin could be attained. 4. Only 1 case showed grade-IV changes, and by treatment it reverted back to grade I (fig. 2). 5. No case showed fused HJ complexes, M patterns, or high-amplitude curves.

Discussion

On admission, all 10 cases showed abnormal ballistocardiograms. Of these 10 cases, 8 showed ballistocardiographic abnormalities even after improvement of anemia, either due to persistence of the previous abnormalities or due to appearance of newer ones during the course of treatment. The abnormalities consisted of small amplitude curves and nonspecific changes in the waves.

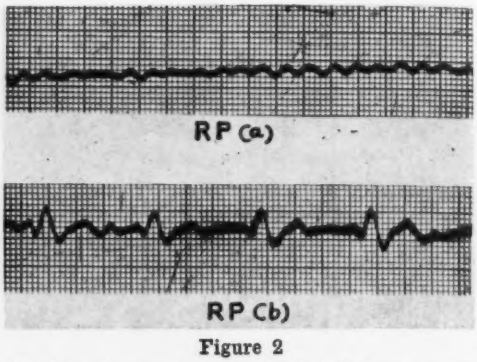

Figure 2

RP (a). Tracing shows grade-IV changes on admission. The hemoglobin level was 3 Gm. per cent. RP (b). After treatment, individual waves are recognizable and normal, except L wave, which is wide.

Table 2

Criteria of Designation of Ballistocardiographic Waves

Waves	Small (if less than) (mm.)	Tall or deep (if more than) (mm.)	Wide (if more than) (sec.)
H	2	3	0.08
I	1	2	—
J	3	5	0.12
K	2	4	0.12
L	2	3	0.12
M	2	2	0.08
N	2	2	0.08

Small Amplitude Curves

On admission, most of the ballistocardiograms showed low-amplitude waves. Such low-amplitude curves, although found in the minority of cases, have also been reported by Sanghvi et al.[2] In physiologic terms, these low-amplitude curves indicate decreased force of cardiac contraction. It has been postulated that the state of chronic severe anemia causes the anoxic myocardial damage that is responsible for the cardiac weakness. On improvement of anemia, curves showed a tendency to revert to normal, owing to elimination of the anoxic factor. Certain tracings were not completely restored to normal, probably due to persistence of anemia as a result of inadequate treatment.

High-amplitude curves in anemia, although not seen in any of our cases, have been re-

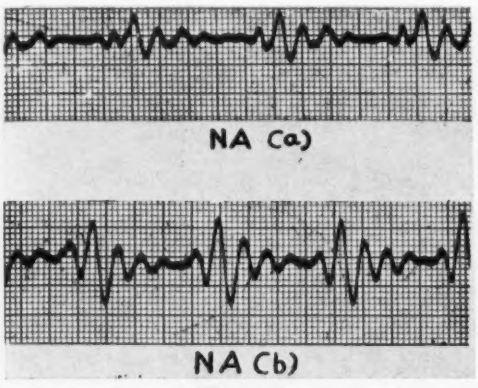

Figure 3

NA (a) and (b) are tracings taken before and after treatment, respectively. Before treatment, H and M waves were small. The other waves were in normal range. After treatment, the complexes showed high-amplitude curves.

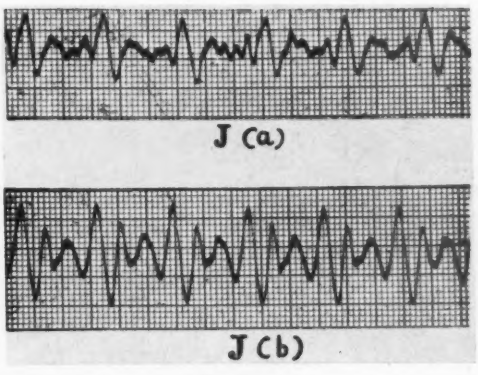

Figure 4

J (a) and (b) are tracings taken before and after treatment, respectively. Prior to treatment, H and M waves were small and L wave was wide. After treatment, all waves show high amplitude.

Table 3

Ballistocardiographic Observations in Ten Patients with Anemia

Case no.	Name	Waves (measured in mm.) H	I	J	K	L	M	N	Remarks
1.	G	S	N	N	N	N	S	S	Before treatment
		N	T	N	N	N	S	S	After treatment
2.	Na	S	N	N	N	—	S	N	Before treatment
		N	T	N	T	T	N	N	After treatment
3.	K	S	N	N	N	S	—	—	Before treatment
		N	N	N	N	T	T	T	After treatment
4.	VP	N	N	T	N	N	S	S	Before treatment
		N	N	T	N	T	S	S	After treatment
5.	M	S	N	N	S	S	S	S	Before treatment
		N	N	N	N	N	N	S	After treatment
6.	S	S	N	S.W	S	—	—	—	Before treatment
		S	N	N	N	S	S	S	After treatment
7.	RP*								Before treatment
		N	N	N	N	N,W	S	—	After treatment
8.	KK	N	N	N	N	—	—	—	Before treatment
		T	N	N	N	W	—	—	After treatment
9.	MM	S	N	S	N	—	—	—	Before treatment
		N	N	N	N	—	—	—	After treatment
10.	J	S	N	T	N	N,W	S	S	Before treatment
		S	N	T	T	N	S	N	After treatment

*Before treatment all complexes show grade IV changes.
—, Absent; N, normal; W, wide; T, tall; S, small.

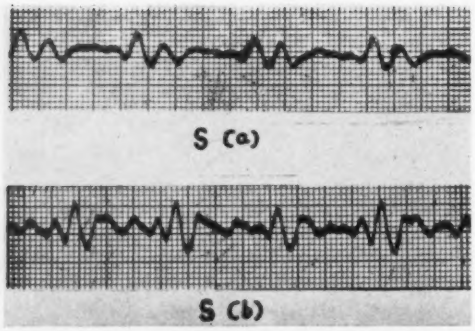

Figure 5

S (a) and (b) are tracings taken before and after treatment, respectively (a) shows small H, I, and K waves. J wave is small as well as slightly wide. After treatment (b) tracings show almost normal amplitudes.

ported by many workers.[1, 2] Besides anemia, large ballistic complexes are also seen in many other cardiovascular diseases of high-output type, like arteriovenous fistulas, thyrotoxicosis, emaciation, patent ductus arteriosus, and certain pulmonary conditions.[5-9] The high-amplitude patterns in these conditions tend to revert to normal when treated. High-amplitude curves in anemia are due to decreased peripheral resistance against which the left ventricle must work. Absence of such curves in the present series was probably due to the more chronic severe nature of anemia, so that the anoxic left ventricle was weakened.

Individual Wave Abnormalities

Various ballistic waves showed nonspecific changes. Prior to treatment, the abnormalities consisted of small H waves; small, tall, wide, or normal J waves; normal or small K waves; and normal, absent, or small LM and N waves. Only 1 case showed grade-IV abnormalities.

In the present series, the H wave was small in 7 cases. De Lalla et al.[10] have analyzed the genesis of the H wave and have suggested that both atrial contraction and the thrust of the heart during isometric contraction are involved in the origin of the H wave. As in chronic severe anemia, both the atrial and ventricular contractions are weakened, due to anoxic myocardial damage, resulting in small H waves. In contrast to findings of Sanghvi et al., no tracings in our series showed tall H waves on admission. These workers believed that tall H waves in their cases were due to increased upward flow of blood in the atria during isometric contraction as a result of anoxic myocardial damage.

The K wave was found to be normal in most of the tracings of our series. Only 2 cases showed small K waves, and these became normal after treatment. It is difficult to decide whether small K waves in these 2 cases were due to decreased peripheral resistance or due to weakened myocardium. Sanghvi et al.[2] found small K waves in most of their cases. These workers have attributed these small K waves to decreased peripheral resistance in anemic patients. Short K waves have also been noted in a variety of other conditions like aortic stenosis,[4] hypotension,[7, 11] coarctation of the aorta,[12] vertical hearts, and thrombosis of the abdominal aorta.[13]

In contrast to findings of Sanghvi et al.[2] none of our cases showed fused HJ complexes, notched I, J, or JK segments, or notched J waves.

On improvement of anemia, a few fresh abnormalities were seen. These consisted of tall H waves (1 case), tall I waves (1 case), tall J waves (3 cases), and tall (3 cases) and wide (2 cases) L waves. In older subjects, known to have heart trouble, Dock et al.[1] also noted the appearance of abnormal ballistic patterns on improvement of anemia. These workers found that only patients without heart disease showed a reversal of high-amplitude curves toward normal without appearance of any fresh abnormality.

Summary

Ballistocardiographic study in 10 cases of chronic severe anemia, with use of Dock's direct body ballistocardiograph, has been reported. The tracings were studied before and after treatment of anemia.

All cases showed abnormal ballistocardiograms. The abnormalities presented no specific pattern. Prior to treatment, in the majority of cases, the waves were smaller than normal.

With few exceptions, the tracings tended to regain their normal size on correction of anemia. No tracings showed fused HJ complexes, tall H waves, notched J waves, M patterns, or high-amplitude curves either before or after treatment.

The present study shows that the state of severe anemia of chronic duration, impairs the mechanical force of cardiac contractions, and, on improvement of anemia, the functional state of the heart improves. Thus, it reflects the usefulness of this new tool in assessing the functional status of the heart in patients with chronically severe anemia.

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This velocity (*systolic*) is only the velocity of the blood at its first entering into the aorta, in the time of *systole;* in consequence of which the blood in the arteries, being forcibly propelled forward, with an accelerated *impetus,* thereby dilates the canal of the arteries, which begin again to contract at the instant the *systole* ceases; by which curious artifice of nature the blood is carried on in the finer capillaries, with an almost even tenor of velocity, in the same manner as the spouting water of some fire-engines is contrived to flow with a more even velocity, notwithstanding the alternate *systoles* and *diastoles* of the rising and falling *embolus* or force.—Stephen Hales, B.D., F.R.S. *Haemastatics,* Vol. II, London, 1733.

Effects of Reduced Glomerular Filtration Rate on Responsiveness to Chlorothiazide and Mercurial Diuretics

By F. C. Reubi, M.D., and P. T. Cottier, M.D.

IT HAS generally been assumed that patients with impaired glomerular filtration would respond to any diuretic in a less satisfactory manner than normal individuals.[1] Many authors believe, for instance, that the unresponsiveness to mercurials in certain cases of severe congestive heart failure is due to a marked decrease in the filtered load of sodium, chloride, and water.[2-4] Evidence, however, is still limited that such a mechanism plays a major role in patients clinically resistant to diuretics. The importance of extrarenal factors, like adrenal cortical hormones, on the tubular reabsorption of sodium should not be underestimated. Patients with nephrotic syndrome and normal glomerular filtration rate may respond very poorly to meralluride, whereas in other subjects the same drug produces a good diuresis in spite of a low glomerular filtration rate.[5] On the other hand, most experiments designed to demonstrate the role of a reduction in glomerular filtration rate on the responsiveness to diuretics have been performed in normal animals, in which the blood supply of the kidney was acutely restricted.[2, 6]

Little work has been done so far to compare the efficacy of diuretics in patients suffering from renal disease with different degrees of functional impairment. The present experiments were designed to investigate the effects of a chronic reduction of the glomerular filtration rate on the responsiveness to chlorothiazide and meralluride.

Material and Methods

Only patients without edema and without heart failure were selected in order to minimize variations due to tubular and extrarenal factors. Since most subjects with low filtration rate had also some degree of arterial hypertension, it was not possible to exclude cases with high blood pressure from this study. It seemed desirable, therefore, to include also hypertensive patients with normal or slightly reduced filtration rate.

Twenty-four individuals were studied. The group consisted of 12 patients with chronic pyelonephritis, 4 with subacute or chronic glomerulonephritis, 3 with essential hypertension, 1 with diabetic glomerulosclerosis, 1 with nephrolithiasis, and 3 subjects without renal disease. Thirteen subjects had a normal blood pressure, 11 had some degree of hypertension. The nonprotein nitrogen was either within normal range or increased.

The study was performed in the morning with the patient remaining in bed. After catheterization of the bladder, a priming infusion of inulin in saline was given intravenously. This was followed by the constant infusion of a solution containing 6 Gm. of inulin in 1,000 ml. of 0.9 per cent sodium chloride. This sustaining infusion was given at a rate of 8 ml. per minute per 1.73 M.^{2}, so that the patient received 1,230 μEq. per minute per 1.73 M.^{2} of sodium during the whole procedure.

Urine and blood samples were first collected in 2 or 3 conventional clearance periods averaging 20 minutes each. In a first group of 12 experiments, chlorothiazide* was then injected intravenously in the dose of 500 mg. per 1.73 M.^{2}. Blood and urine collections were continued over 4 periods of 40 to 45 minutes. In a second group of 7 experiments, meralluride was given in the dose of 2 ml. per 1.73 M.^{2} (= 176 mg. per 1.73 M.^{2}) after the 2 control periods. Urine and blood samples were collected over 5 more periods of 40 to 45 minutes. Since the peak action was not attained before 1½ to 2 hours, only the results of the last 3 periods have been considered.

In another group of 5 experiments, meralluride was given as in group 2. But 80 to 90 minutes later the patient also received 500 mg. per 1.73 M.^{2} of chlorothiazide. Three more collection periods of 40 to 50 minutes followed the injection.

The blood pressure was measured frequently by the auscultatory technic. Blood and urine samples were analyzed for inulin, sodium, potassium, and chloride. Clearances were calculated by standard methods. Inulin was determined by the method of Schreiner,[7] sodium and potassium with an internally standardized flame photometer, chloride by the method of Lang.[8]

From the Medical Policlinic, University of Berne, Switzerland.

*Kindly supplied by Merck, Sharp & Dohme, West Point, Pennsylvania.

Results

Experiments with Chlorothiazide Alone (Table 1)

Effect on Blood Pressure

In no case was a significant hypotensive effect observed during the 3 hours following the injection.

Effect on Glomerular Filtration Rate

After chlorothiazide there was a moderate decrease in 6 patients, the greatest drop observed being 17.7 per cent. In 1 patient the glomerular filtration rate increased 25.3 per cent. In the remaining patients there was no change at all. For the whole group the mean was a decrease of 7 per cent.

Effect on Urinary Flow and Water Reabsorption (Fig. 1)

Under control conditions the urinary flow was not related to the glomerular filtration rate. In all patients with a glomerular filtration rate above 15 to 20 ml. per minute, chlorothiazide elicited a prompt diuretic response. In most cases the highest rate of urinary flow was already reached during the first period after injection. In the following periods the diuresis was either sustained or decreased slowly. The highest urinary flow was observed in patient 2, with an inulin clearance of 123 ml. per minute. But in most patients with a glomerular filtration rate above 15 to 20 ml. per minute the urinary flow after chlorothiazide increased to 4 to 6 ml. per minute, these values bearing no relationship to the glomerular filtration rate itself. In patients with a very low glomerular filtration rate, however, the diuretic response was poor (patients 11 and 12).

When the tubular reabsorption of water is calculated from these data, it appears that with decreasing glomerular filtration rate the drug blocks an increasing fraction of the water reabsorption, so that at different levels of glomerular filtration rate the diuretic effect remains of the same order of magnitude. The tubular reabsorption obviously cannot be blocked by more than 40 per cent of the filtered water load. At this point a further drop in glomerular filtration rate results in a sharp decrease in the diuretic effect.

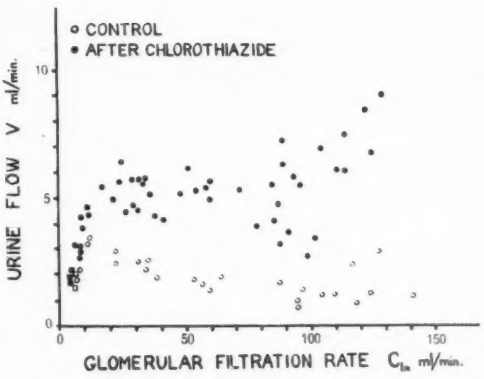

Figure 1

Urinary flow before and after chlorothiazide (500 mg. intravenously) in 13 patients with different rates of glomerular filtration. Each point represents a urine collection period. The case with the lowest filtration rate (squares) received both chlorothiazide and meralluride.

Effect on Sodium and Chloride Excretion and Reabsorption

In these experiments sodium and chloride behaved similarly and can be considered together (figs. 2 and 3). The control excretion of these electrolytes was variable but unrelated to the filtered load. In most cases the saluretic response after chlorothiazide paralleled the diuretic response. While the greatest sodium and chloride outputs were observed in patient 2, with a high filtration rate, no significant differences in saluresis were seen in the other patients with rates of glomerular filtration ranging between 20 ml. per minute and normal values. A further reduction of the glomerular filtration rate below 15 to 20 ml. per minute resulted in a sharp decrease in the saluretic effect. Nevertheless, some effect was still present in all cases, even in patient 12.

The fraction of filtered sodium and chloride rejected at the tubules increased progressively with decreasing filtered load. The total amount of these electrolytes rejected by the tubules after chlorothiazide appears to be limited to about 30 to 35 per cent of the filtered load. At this point a further decrease in glomerular filtration rate is followed by a sharp decrease in saluresis.

Table 1

*Effects of Chlorothiazide in Twelve Patients**

Patient		Period No.	Blood pressure mm. Hg	Urine flow ml./min.	GFR† ml./min.	Tubular rejection of water %	Sodium			Chloride			Potassium
							Excreted μ Eq./min.	Filtered μ Eq./min.	Tubular rejection %	Excreted μ Eq./min.	Filtered μ Eq./min.	Tubular rejection %	Excreted§ μ Eq./min.
1. F. S.	Control	1-3	120/65	1.19	125	0.95	81	16,900	0.5	123	13,000	0.9	66
	After C‡	4-7	123/73	4.54	107	4.2	655	16,100	4.1	627	11,900	5.2	229
2. S. d. M.	Control	1-2	168/113	2.69	123	2.2	389	17,200	2.3	472	13,000	3.6	105
	After C	3-6	158/115	7.99	124	6.5	1223	17,300	7.1	1105	13,400	8.2	216
3. F. F.	Control	1-2	110/79	1.02	111	0.92	159	15,750	1.0	158	10,900	1.4	32
	After C	3-6	109/78	6.50	92	7.0	1003	13,000	7.7	860	9,700	8.8	124
4. L. L.	Control	1-2	137/71	0.85	94	0.9	177	13,700	1.3	184	9,950	1.8	41
	After C	3-6	141/86	3.68	86	4.3	842	12,420	6.8	685	9,300	7.3	103
5. B. V.	Control	1-2	154/97	1.57	89	1.8	228	12,700	1.8	281	9,200	3.0	73
	After C	3-6	170/108	5.35	87	6.1	929	12,290	7.5	760	9,000	8.4	129
6. L. J.	Control	1-2	124/76	1.71	62	2.8	160	8,600	1.9	188	7,100	2.6	36
	After C	3-6	127/74	5.24	59	8.9	551	8,160	6.8	568	6,180	9.1	126
7. R. J.	Control	1-2	229/100	1.70	54	3.1	304	7,700	3.9	336	5,700	5.9	33
	After C	3-6	212/109	4.84	45	10.7	790	6,400	12.4	711	4,860	14.6	94
8. P. Z.	Control	1-2	150/100	2.04	37	5.5	245	5,100	4.8	224	4,060	5.5	27
	After C	3-6	154/102	4.66	31	15.0	576	4,340	13.3	504	3,450	14.6	62
9. I. H.	Control	1-2	165/101	2.46	32	7.7	281	4,530	6.2	302	3,580	8.4	59
	After C	3-6	158/98	5.70	32	17.8	716	4,540	15.8	701	3,630	19.3	90
10. M. H.	Control	1-2	137/101	2.69	22	12.2	282	3,390	8.3	286	2,480	11.5	44
	After C	3-6	144/99	5.61	22	25.6	649	3,180	20.5	593	2,450	24.2	51
11. H. W.	Control	1-2	239/110	3.33	11	30.0	336	1,590	21.0	316	1,390	22.6	38
	After C	3-6	239/110	4.21	10.5	40.1	467	1,500	31.1	457	1,205	37.6	35
12. A. Z.	Control	1-2	172/108	1.95	6.3	31.0	143	870	16.4	148	677	21.8	45
	After C	3-6	190/110	2.92	7.9	37.0	256	1,112	23.0	284	892	31.7	58

*Figures are average values of several periods.

†Glomerular filtration rate (inulin clearance).

‡After chlorothiazide, 500 mg. intravenously.

§Only the first 2 periods after chlorothiazide have been considered in this column.

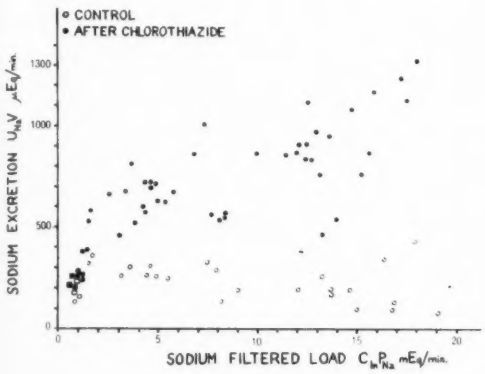

Figure 2

Sodium excretion before and after chlorothiazide in 13 patients (same experiments as in fig. 1).

Effect on Potassium Excretion

Whereas the diuretic and saluretic effect after chlorothiazide was usually sustained and lasted during the whole experiment, the kaliuretic effect was of short duration and obvious only during the first 2 periods after injection of the drug. We have, therefore, considered only these 2 periods in table 1 and figure 4. From our data the degree of kaliuresis after chlorothiazide appears almost proportional to the glomerular filtration rate. At low filtration rates there was no increase in kaliuresis above the control values.

Experiments with Meralluride Alone (Table 2)

There was no consistent change in blood pressure. In most cases a slight increase in glomerular filtration rate was observed. Although a kaliuretic effect was entirely lacking, the diuretic and saluretic response was very similar to that seen after chlorothiazide.

Effect on Urinary Flow and Water Reabsorption

Under control conditions the urinary flow was not related to the glomerular filtration rate (fig. 5). In all patients with a glomerular filtration rate greater than 10 ml. per minute, the diuretic response to meralluride was of the same order of magnitude, ranging from 4.96 to 8.88 ml. per minute. This means that meralluride, like chlorothiazide, blocks a fraction of the tubular reabsorption of water that increases more or less proportionately to the decrease in filtration rate. The highest value for the tubular rejection of water in this series was 48.6 per cent.

Effect on Sodium and Chloride Excretion and Reabsorption

The control excretion of these electrolytes was not related to the glomerular filtration rate (figs. 6 and 7). After meralluride, the saluretic effect was comparable in all cases with a glomerular filtration rate greater than 15 to 20 ml. per minute. In the 2 patients with a glomerular filtration rate of about 12 ml. per minute, the saluretic effect was still present but of lower magnitude. It seems, therefore, that the tubular rejection of sodium and chloride increases after meralluride more or less proportionally to the decrease in filtered load. The highest values observed in these experiments were 39.5 per cent for sodium and 41.5 per cent for chloride.

Effect on Potassium Excretion

The control excretion was unrelated to the glomerular filtration rate. After meralluride there was, as a rule, a significant decrease, averaging for the whole group 26 per cent.

Experiments with Meralluride and Chlorothiazide (Table 3)

Effect on Glomerular Filtration Rate

In most cases there was some decrease, averaging 10 per cent for the whole group.

Effect on Urinary Flow and Water Reabsorption

In the 2 patients with normal glomerular filtration rate, the diuretic effect of chlorothiazide was markedly enhanced by the previous administration of meralluride. The comparison of the rates of urinary flow observed in these subjects with data on patients receiving chlorothiazide alone or meralluride alone, suggests a summation of the individual effects. But in 2 patients with a moderate reduction of the glomerular filtration (58 and 30.6 ml. per minute) the diuretic response to both drugs given together was not greater than after meralluride alone. In patient 5, with a very low filtration rate, there was practically no diuretic effect, the decrease in water reabsorption being compensated by the decrease in water filtration. The rejected frac-

Table 2

*Effects of Meralluride in Seven Patients**

Patient	Period No.	Blood pressure mm. Hg	Urine flow ml./min.	GFR† ml./min.	Tubular rejection of water %	Sodium			Chloride			Potassium
						Excreted μ Eq./min.	Filtered μ Eq./min.	Tubular rejection %	Excreted μ Eq./min.	Filtered μ Eq./min.	Tubular rejection %	Excreted μ Eq./min.
1. W. Z. Control	1-2	128/63	1.10	135	0.82	235	18,500	1.3	256	14,100	1.8	75
After M‡	5-7	132/70	8.88	154	5.7	1460	21,250	6.9	1420	16,200	8.8	53
2. M. M. Control	1-2	142/80	2.82	127	2.2	220	17,300	1.3	263	12,750	2.1	58
After M	5-7	150/85	4.96	114	4.4	837	15,900	5.3	877	12,200	7.2	35
3. H. P. Control	1-2	128/80	0.94	100	0.94	185	13,800	1.3	244	10,600	2.3	68
After M	5-7	128/85	6.62	103	6.4	1270	14,100	9.0	1270	10,900	11.6	46
4. R. B. Control	1-2	160/123	3.20	49	6.5	262	6,350	4.1	263	4,880	5.4	70
After M	5-7	168/120	6.39	48.3	13.2	823	6,500	12.7	817	5,250	15.5	64
5. E. S. Control	1-2	110/78	1.79	38.4	4.7	141	5,300	2.7	222	4,140	5.4	55
After M	5-7	115/83	8.70	43.3	20.1	1130	5,940	19.0	1170	4,670	25.0	33
6. R. S. Control	1-2	150/80	1.98	12.5	15.8	131	1,705	7.7	212	1,495	14.2	47
After M	5-6	150/90	6.76	18.5	36.6	812	2,525	32.0	890	2,205	40.0	46
7. R. G. Control	1-2	250/110	3.90	11.9	33.0	355	1,570	22.6	362	1,395	26.0	41
After M	5-7	240/100	6.18	12.7	48.6	673	1,700	39.5	634	1,530	41.5	28

*Average values of 2 or 3 periods. The first 2 periods following the injection were left out, as the maximal effect was not attained at this time.
†Glomerular filtration rate (inulin clearance).
‡After meralluride, 2 ml. intravenously.

Table 3

*Diuretic and Saluretic Effect of Meralluride Combined with Chlorothiazide in Five Patients**

Patient	Period No.	Blood pressure mm. Hg	Urine flow ml./min.	GFR† ml./min.	Tubular rejection of water %	Sodium			Chloride			Potassium
						Excreted μ Eq./min.	Filtered μ Eq./min.	Tubular rejection %	Excreted μ Eq./min.	Filtered μ Eq./min.	Tubular rejection %	Excreted μ Eq./min.
1. T. A. Control	1-2	140/70	3.89	137	2.8	471	19,200	2.5	422	14,300	3.0	49
After M + C‡	5-7	130/85	10.76	119	9.0	1830	16,800	10.9	1465	13,400	10.9	54
2. I. M. Control	1-2	120/55	1.94	129	1.5	100	18,500	0.5	150	13,700	1.2	88
After M + C	5-7	118/63	14.63	106	13.7	2360	15,250	15.5	2220	11,250	19.7	56
3. E. J. Control	1-2	113/65	1.17	58	2.0	123	8,100	1.5	168	6,450	2.6	30
After M + C	5-7	110/63	4.93	52.5	9.4	700	7,600	9.2	640	5,890	10.9	35
4. F. K. Control	1-2	135/80	4.39	30.6	14.2	268	4,080	6.6	284	3,250	8.7	50
After M + C	5-7	140/90	7.91	33.6	23.3	1002	4,517	22.1	959	3,755	25.5	29
5. M. F. Control	1-2	233/138	1.79	5.9	30.3	211	834	25.3	156	600	26.0	21
After M + C	5-7	233/130	1.94	4.4	44.0	231	597	38.8	196	457	42.8	26

*Average values of 2 or 3 periods. Periods between the 2 injections have been left out.
†Glomerular filtration rate (inulin clearance).
‡After meralluride, 2 ml. intravenously, and chlorothiazide, 500 mg. intravenously 80 to 90 minutes later.

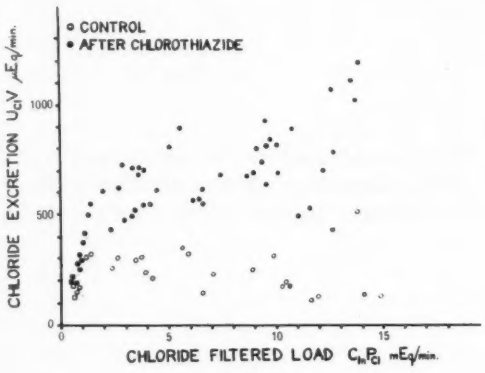

Figure 3

Chloride excretion before and after chlorothiazide in 13 patients (same experiments as in figs. 1 and 2).

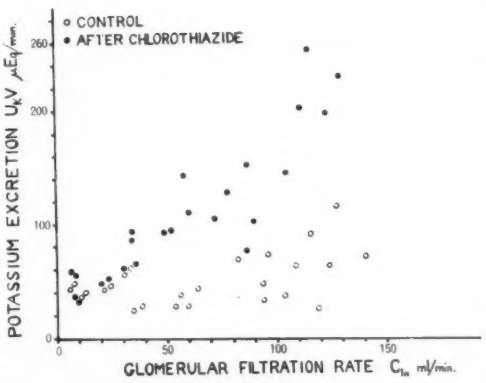

Figure 4

Potassium excretion before and after chlorothiazide in 12 patients. The kaliuretic action is proportional to the glomerular filtration rate.

tion of filtered water seemed to be limited to 44 per cent.

Effect on Sodium and Chloride Excretion and Reabsorption

The saluretic effect of chlorothiazide was also markedly enhanced by the previous administration of the mercurial in the 2 patients with normal glomerular filtration rate, suggesting summation of the individual effects. The 2 patients in whom the glomerular filtration was moderately reduced showed a response comparable to that seen after meralluride alone. In patient 5 the saluretic effect was very slight. Tubular rejection of sodium and chloride seemed to be limited to 38.8 and 42.8 per cent of the filtered load, respectively.

Effect on Potassium Excretion

In no case could a kaliuretic effect be observed. There was a rather slight decrease in the excretion of potassium, averaging 6 per cent for the whole group. It would appear, therefore, that the previous administration of meralluride is capable of inhibiting the kaliuretic properties of chlorothiazide, which in turn prevents a marked drop in potassium excretion, as seen after meralluride alone.

Discussion

In discussing the effects of a reduction of the glomerular filtration rate on the responsiveness to diuretic agents, we must consider not only the decrease in the filtered amount of sodium, chloride, and water but also the extent to which their tubular reabsorption can be blocked by these drugs. Furthermore, we must take in account that in patients with reduced glomerular filtration rate, but without edema, there is already a marked permanent decrease in tubular reabsorption under basal conditions and during loading with saline as well. This decrease is roughly proportional to the reduction of the inulin clearance, so that comparable amounts of salt and water are still excreted at any level of glomerular filtration (fig. 9, dotted line O), as long as renal functions are not too severely impaired.

The mechanism of action of diuretic agents is not easily understood. At least three different possibilities may be considered. First, it could be assumed that chlorothiazide and meralluride block the tubular reabsorption up to an invariable percentage of the filtered load. This would imply a decrease in the diuretic and saluretic responses proportional to the reduction of the glomerular filtration rate (fig. 9, straight line A). There is some evidence that such a mechanism does operate under certain experimental conditions. Davidson et al.[6] found in the dog that mechanical compression of one renal artery would reduce the sodium excretion *more* than the filtration rate (fig. 9, line B′). However, when Salyrgan

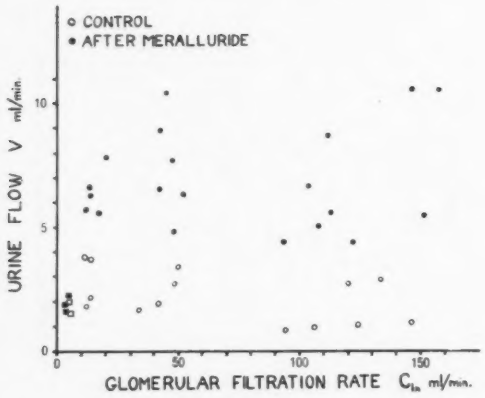

Figure 5

Urinary flow before and after meralluride (176 mg. intravenously) in 8 patients with different rates of glomerular filtration. One patient (squares) also received chlorothiazide.

was given in similar experiments, mechanical reduction of the filtration rate was followed by a proportional decrease in the sodium excretion (fig. 9, line A′). In representative experiments, the calculated tubular rejection of sodium (assuming a plasma sodium of 140 mEq. per liter) was, on the constricted side, 14.4 per cent before and 15.8 per cent after clamping, on the other side 14.1 per cent and 16.2 per cent, respectively, which is practically identical. Somewhat different results have been reported by Pitts and Duggan.[2] By compressing the aorta of dogs receiving large doses of a mercurial diuretic, these authors produced a reduction of the sodium excretion greater than that of the glomerular filtration rate, the tubular rejection decreasing from 20 to 10 per cent of the filtered load (fig. 9, line B).

Results of acute experiments in normal animals suggest therefore that lowering of the glomerular filtration rate during mercurial saluresis decreases the excretion of sodium correspondingly or even to a greater extent. Should this hold true in patients with chronically reduced filtration rate, the regression curves A and B would intercept the straight line 0 at relative high levels of filtration. Below this level, there should be a complete loss of diuretic response. It appears clear from our figures (figs. 1 to 3 and 5 to 8) that this is not so; even at very low filtration rates, some diuretic and saluretic effects still occur.

A second possibility is also conceivable, at least theoretically: the drug would block a fixed percentage of the tubular reabsorption in addition to the variable rejected fraction responsible for the control excretion. This would mean a great diuretic response at high filtration levels, because in these cases the control values of tubular rejection are very small, but only a slight increase at low filtration levels, where the rejected fraction is already large (fig. 9, tracing C). However, there is no definite evidence that this possibility applies to acute experiments or to patients receiving meralluride or chlorothiazide alone. Our data show that the additional fraction of tubular reabsorption blocked by meralluride or chlorothiazide is not constant, but increases with the reduction of glomerular filtration rate. Only those few experiments performed with a combination of both diuretics suggest some kind of proportional relationship of this type. The existence of a curvilinear correlation cannot be excluded, however, with so little data on hand.

Finally, a third mechanism may be involved: the diuretic agent might increase by a constant multiplying factor the fraction of the filtered load already rejected under control conditions. For instance, chlorothiazide would produce a 3-fold increase at any level of tubular rejection. In a case with a glomerular filtration rate of 100 ml. per minute and a tubular rejection of 1 per cent, the rejected amount would increase to 3 per cent. In a case with a glomerular filtration rate of 25 ml. per minute, and tubular rejection of 4 per cent, the latter would increase to 12 per cent. It follows that the excretion of sodium, chloride, and water after chlorothiazide would be similar in both cases (fig. 9, tracing D). A further drop in glomerular filtration rate to 3 ml. per minute should, however, limit the effectiveness of this mechanism, as a 3-fold increase in the control rejection of 33 per cent should bring it up to 100 per cent. Be-

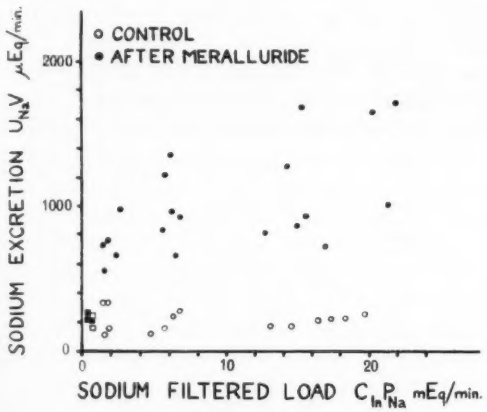

Figure 6

Sodium excretion before and after meralluride in 8 patients (same experiments as in fig. 5).

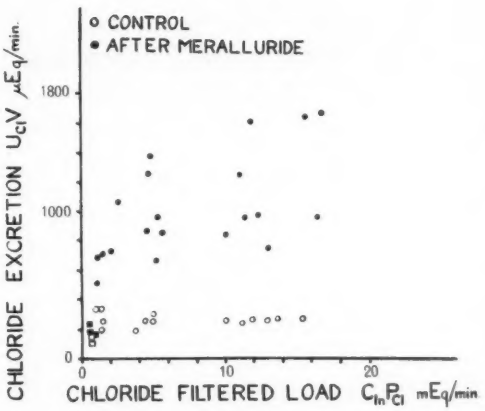

Figure 7

Chloride excretion before and after meralluride in 8 patients (same experiments as in figs. 5 and 6).

low this critical level of glomerular filtration, the excretion of sodium, chloride, and water should fall very sharply. As it is very unlikely that tubular reabsorption can be blocked completely by any diuretic agent, we might assume a more reasonable limit, for instance 40 per cent (fig. 9, line E). Our data on chlorothiazide and meralluride alone certainly seem to fit this last hypothesis best. While such a mechanism cannot be easily understood, we must recognize that in our observations the decrease in responsiveness to diuretic agents is much less than one would expect from the reduction in filtration rate, should the blocked fraction of tubular reabsorption remain constant. As a matter of fact, our experimental data are more consistent with the assumption of a 2-to-3-fold increase in the fraction rejected prior to the administration of chlorothiazide or meralluride. But the total rejection cannot exceed a certain limit and its maximum seems to lie at about 30 to 40 per cent of the filtered load. The highest figures observed after chlorothiazide are 40.1 per cent for water, 31.1 per cent for sodium, and 37.6 per cent for chloride. After meralluride these figures are 48.6, 39.5, and 41.5 per cent, respectively. Even when both drugs are combined, water reabsorption can be blocked only to 44 per cent, sodium to 38.8 per cent, and chloride to 42.8 per cent. It would seem desirable to have more data on patients with a very low filtration rate, in order to determine these limits and draw the lower part of the experimental curve with a reasonable degree of accuracy. Unfortunately, patients with a glomerular filtration rate of about 5 ml. per minute are markedly azotemic and may tolerate the experimental procedure rather poorly. Anyway, our figures are very close to the value found by Pitts[9] in the normal dog for the maximal fraction that can be blocked by the combined action of mercurials and chlorothiazide.

In figure 9 we have drawn the experimental curve F as a coarse visual approximation from data in tables 1 and 2. This curve lies rather close to the tracing DE, differing from the latter only in two respects: the line F shows a smooth inflexion instead of the sharp angulation seen in tracing DE and its upper part is neither linear nor quite horizontal. We believe that these differences can be best explained by assuming a certain dispersion in the glomerulo-tubular activity. A comparison with glucose titration curves obtained by Smith[10] in hypertensive patients and by ourselves[11] in patients with renal diabetes indicates that such a mechanism may also play a role in the present experiments. This would imply that the single tubules are not rejecting exactly the same fraction of the filtered

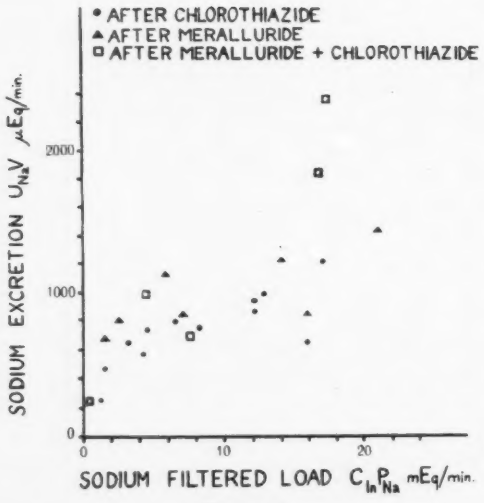

Figure 8

Comparative excretion of sodium after chlorothiazide (circles), meralluride (triangles), and both drugs given together (squares). Each point represents the average of several periods in 1 patient.

load, or that they are receiving from the corresponding glomeruli slightly different loads.

The observation that mercurials may enhance the diuretic and saluretic effects of chlorothiazide has already been made by others.[9, 12] It may be concluded that the two drugs block two different reabsorptive mechanisms or the same mechanism in two different ways.[9] It is of interest, however, that at very low filtration rates the maximal fraction of the tubular reabsorption that can be blocked by chlorothiazide or meralluride alone is not increased when both drugs are given together (patient 5). In 2 patients with a moderate reduction of the glomerular filtration rate the effect of the combination was within the usual range of response to the individual drugs. Only in the 2 patients with normal glomerular filtration rate were the saluretic and diuretic actions of chlorothiazide markedly enhanced by the previous administration of meralluride, suggesting summation of the individual effects. Obviously, the potentiation of chlorothiazide by mercurials is of practical significance in cases with a high glomerular filtration rate only.

We have made no attempt to correlate further the response to the combination of both drugs with the level of the glomerular filtration. While a few points on figure 9 are suggestive of direct proportionality, we consider that a curvilinear relationship cannot be ruled out. Such a tracing might result from the summation of the individual curves observed with chlorothiazide or meralluride alone, which would increase the splay correspondingly.

The striking influence of a chronic reduction of the glomerular filtration upon the kaliuretic effect of chlorothiazide is not too surprising. The simplest explanation of our findings is to assume that the increased tubular rejection of sodium observed at low filtration rates leaves only a small amount of this electrolyte available for exchange with potassium. The observation that the kaliuretic response decreases almost proportionately to the glomerular filtration rate is not in agreement with the data reported in animals.[6] But the discrepancy between the results in animals and our data may arise from the different behavior of the rejected fraction of sodium in the two types of experiments: this fraction was increased in our patients, but decreased or was unchanged in the dogs.[6]

The inhibitory effect of mercurials on chlorothiazide kaliuresis might be due to a similar mechanism. The previous administration of meralluride enhances the natriuretic properties of chlorothiazide and increases the tubular rejection of sodium. This might reduce the amount of sodium available for exchange with potassium and therefore decrease the excretion of the latter. An alternative and perhaps more likely explanation is to attribute to mercurial compounds a specific inhibitory effect on the potassium secretion itself.[13] It should be kept in mind, however, that under clinical conditions, mercurial agents do not always block the excretion of potassium. Patients with cirrhosis of the liver and nephrotic syndrome may respond to meralluride with an increased potassium output, instead of saluresis.[5]

The practical significance of our findings is

subject to certain limitations due to the short duration of the experiment and to the fact that only patients with diseased kidney but without edema have been examined. We think, however, that our results may have some clinical implications. The peak response to 2 ml. of meralluride is somewhat greater than that observed after 500 mg. of chlorothiazide, but there is a considerable overlapping of both ranges of responses. After chlorothiazide the effect is immediate; after meralluride the peak action is delayed but may last longer. It would appear, therefore, that in patients with a chronic reduction of the glomerular filtration rate, both drugs give comparable diuretic and saluretic results. These results depend upon renal and extrarenal factors. Over a wide range, i.e., from 15 to 20 ml. per minute up to normal values, the level of glomerular filtration is of little significance, when chlorothiazide or meralluride are used alone. Only at very low filtration rates is the saluretic effect markedly impaired. These facts seem to indicate that in the course of most chronic renal diseases without edema there is a functional adaptation of the reabsorptive mechanisms to the reduced glomerular activity, not only under basal conditions, but also after administration of a diuretic. This is in good agreement with the observation that the diseased kidney may retain its ability to concentrate and to dilute urine.[14]

The applicability of our findings to the problem of the refractoriness to diuretics in congestive heart failure remains open to question. The assumption, that in these patients the lack of response is due to a very low filtration rate, rests mainly upon acute experiments in normal dogs and would need more adequate support. On the other hand, our results show that a permanent reduction of the filtration rate per se has little influence on the diuretic response, provided the fraction of the filtered sodium rejected under basal conditions is large. In patients with cardiac or nephrotic edema this fraction is very small and even a 4-fold increase will not lead to a marked saluresis. The refractoriness to diuretics, therefore, can best be correlated with a reduction of the rejected fraction. This in turn depends largely on extrarenal factors rather than on the level of filtration.

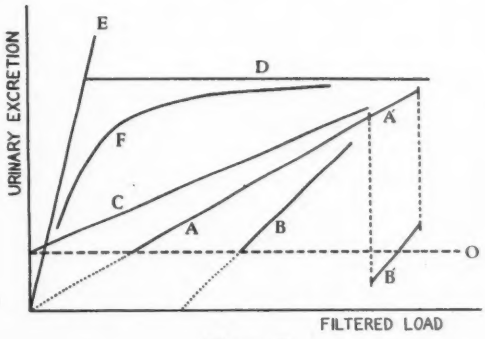

Figure 9

Possible relationships between excretion and filtered load of water, sodium, and chloride after chlorothiazide or meralluride. Tracing F is drawn from experimental data in tables 1 and 2.

The well-known kaliuretic effect of chlorothiazide, which may be very disturbing during the course of sustained therapy, becomes less important when the glomerular filtration is substantially reduced. Since meralluride appears to be capable of blocking this effect and also markedly enhances the saluretic properties of chlorothiazide in patients with high filtration rate, the combination of both drugs seems to be advisable in such patients.

Finally, it must be noted that a single injection of chlorothiazide does not lower the arterial blood pressure, even in hypertensive patients. This is in agreement with observations made by others.[15] Our patients were studied, however, under conditions of loading with saline, which may well explain the lack of any hypotensive effect related to saluresis.

Summary

Clearance experiments have been performed in 24 subjects with different levels of glomerular filtration, suffering from renal disease without edema, in order to compare the diuretic, saluretic, and kaliuretic responses to a single intravenous injection of meralluride, chlorothiazide, or both together. The inulin clearances of these patients ranged from 5.9 to 135 ml. per minute. The effects of the

drugs were studied under constant loading with saline over 3 hours after injection.

Our results indicate that over a wide range (15 to 20 ml. per minute up to normal values) a permanent reduction of the glomerular filtration rate has little influence on the diuretic and saluretic effects of meralluride or chlorothiazide. Below 15 to 20 ml. per minute a further reduction results in a sharp decrease in the diuretic and saluretic actions. This can be best explained by assuming that the diuretic agents block an increasing fraction of the tubular reabsorption of water, sodium, and chloride related to the decrease in glomerular filtration rate. This fraction, however, seems to be limited to 30 to 40 per cent of the filtered load. Some dispersion in the glomerulo-tubular activity may account for the splay of the experimental curves.

The kaliuretic effect of chlorothiazide is proportional to the glomerular filtration rate. This effect can be blocked by meralluride.

At high levels of glomerular filtration the diuretic and saluretic actions of meralluride and chlorothiazide are additive. At lower levels of filtration, such a summation effect is not demonstrable. Apparently, both drugs given together cannot block the reabsorption of more than 30 to 40 per cent of the filtered load.

A single injection of chlorothiazide does not lower the arterial blood pressure of hypertensive subjects, loaded with saline, but produces a slight decrease in the glomerular filtration rate, averaging 7 per cent.

Acknowledgment

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The Antihypertensive Actions of Benzothiadiazines

By BERTRAM M. WINER, M.D.

THE PRECISE mechanisms by which low-sodium diets,[1] diuretics,[2-4] and low-potassium diets[5] are antihypertensive have not been established. Recent studies have suggested that reductions in plasma and extracellular fluid volumes play an important part in the antihypertensive action of chlorothiazide.[6-8] The present studies were undertaken to elucidate the separate roles of the depletions of sodium, potassium, plasma volume, and extracellular fluid volume in the hypotensive action of benzothiadiazines. The magnitudes of the deficits, the general sites of the losses, the effects of added salt, and the effects of repletion of plasma volume were examined.

Materials and Methods

All subjects had sustained hypertension and grade two fundi (Keith-Wagener scale), without edema or renal insufficiency. Dietary sodium was not restricted.

Plasma volume was determined from two venous samples drawn without stasis 12 to 18 minutes after injection of I^{131}-tagged human serum albumin.[9, 10] The radioactivity of heparinized plasma samples and diluted injected solution was measured with a well-type scintillation counter. Twenty-four-hour exchangeable potassium and 24-hour exchangeable sodium were determined simultaneously by the differential counting technic of Robinson.[11] For single determinations of exchangeable sodium a scintillation counter was used; a dip counter was used for single determinations of exchangeable potassium. Serum or plasma samples were counted to a minimum of 10,000 counts. Urine was counted to 5,000 counts. Serum and urine sodium and potassium concentrations were determined with a flame photometer. Extracellular fluid volume was measured with thiosulfate;[12] four aliquots of venous blood were drawn at intervals of 10 minutes in the period 30 to 60 minutes after injection. All measurements were carried out in duplicate. Test substances were given in calibrated syringes.

All blood pressures were determined by the same technician by the auscultatory technic. During each visit in the laboratory blood pressure was measured in the sitting position at intervals of a few minutes for approximately 30 minutes. The average of the lowest two blood pressures was taken to represent the blood pressure of the day. Patients were seen at intervals of 1 to 14 days. The blood pressures of the last two visits of a period of study were averaged to represent the response of that period. In the study of the effects of re-expansion of plasma volume by intravenous infusion of Dextran, blood pressure was determined at intervals of a few minutes for 30 minutes before and 120 minutes after each infusion.

Results

Effects of Chlorothiazide

After 6 to 8 weeks of administration of chlorothiazide in daily doses of 0.75 to 1.5 Gm. (table 1) blood pressure was reduced more than 10 per cent in 16 of 20 patients. Reserpine, which had been given to 10 patients daily for months, was continued throughout this study. For the group as a whole blood pressure fell from 191/108 mm. Hg to 158/93 mm. Hg ($p<.001$).

Body weight decreased an average of 1.2 ± 1.8 Kg. ($p<.01$). The thiosulfate space, a measure of extracellular fluid,[12, 13] was reduced an average of 1.1 L. ($p<.05$). Twenty-four-hour exchangeable sodium fell 137 ± 161 mEq. ($p<.01$), although serum sodium concentration was unchanged. Plasma volume was reduced an average of 155 ± 271 ml. ($p<.05$), a change of 6 per cent. There was no consistent relationship between the changes in exchangeable sodium or plasma volume and the arterial pressure changes.

Twenty-four-hour exchangeable potassium decreased an average of 165 ± 256 mEq. ($p<.05$) (table 1). Serum potassium fell from 4.2 to 3.4 mEq. per liter ($p<.001$). Pretreatment extracellular fluid volume averaged 12 liters. There was a loss of approximately 10 mEq. of potassium from the extra-

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Table 1

The Effects of Six to Eight Weeks of Chlorothiazide Therapy

Patients	Before chlorothiazide	Blood pressure mm. Hg after chlorothiazide	Change	Weight Kg.	Extracellular fluid volume L.	Plasma volume ml.	24-Hour exch. sodium mEq.	Serum sodium mEq./L.	24-Hour exch. potassium mEq.	Serum potassium mEq./L.
H. P.	216/114	152/85	−64/−29	−0.2		−416	−72	+2.0	−229	−0.7
J. S.	210/102	164/74	−42/−28	−0.1	−3.3	−627	−150	+0.8	−568	−0.1
A. K.	184/122	148/102	−36/−20	−2.6		−317	−15	+2.3		−0.5
I. F.	188/104	156/96	−32/−8	−1.3	±0.0	−663	−139	+5.7	−421	−0.9
M. K.	170/108	146/92	−24/−16	−6.7	−1.1	−115	+52	−3.5	−511	−1.0
M. M.	193/93	170/82	−23/−13	−3.9		−15	−50	−1.8	−42	−1.4
I. R.	167/115	147/102	−20/−13	−0.4	−0.4	−170	−127	−4.9	+ 3	−0.5
F. Z.	209/106	193/97	−16/−9	+0.3			−113	−3.0	−134	−0.3
L. P.	184/112	171/104	−13/−8	0.0	−1.3	−291	+65	0.0	−360	−1.1
L. A.	194/127	175/127	−19/−3	+0.5		+144	−130	−1.1	−40	−0.1
C. J.	172/100	119/74	−53/−26	−1.0		+83	−33	+2.8	−499	−1.1
M. L.	176/109	125/82	−51/−27	−3.6		+125	−211	−2.5	−19	−0.5
L. C.	201/103	146/87	−55/−16	−0.7			−89	−1.9	+378	−0.6
F. B.	212/102	161/89	−51/−13	−0.3	−1.4	+92	−51	+0.9		−0.4
M. L.	200/120	166/98	−34/−22	−1.6		+44	−199	−3.6	−93	−0.2
S. G.	176/99	140/85	−36/−14	+0.6	+0.9	+227	−42	−0.9	+107	−0.6
C. M.	178/90	152/74	−26/−16	−0.8		−131	−149	−0.5	−15	−0.9
H. A.	148/90	121/81	−27/−9	−0.6	−2.0	+82	−544	−2.7		−0.8
G. M.	192/98	165/87	−27/−11	−2.0	−2.5	−274	−180	−4.3	−203	−1.6
W. R.	244/146	240/144	− 4/−2	+0.8	±0.0	−560	−562	−2.3		−0.6
Mean	191/108	158/93	−33/−15	−1.2	−1.1	−155	−137	−0.9	−165	−0.7
Standard deviation			±15.8/±8.0	±1.84	±1.27	±271	±161	±2.70	±256	0.42
p			<.001/<.001	<.01	<.05	<.05	<.01	> .1	<.05	< .001

Table 2

Effects of the Addition of Twenty Grams of Sodium Chloride Daily during Continuous Administration of Hydrochlorothiazide or Chlorothiazide

Patient	Blood pressure mm. Hg			Changes				
				Weight Kg.		24-Hour urinary sodium mEq.	24-Hour exch. K mEq.	
	Before thiazide	After thiazide	After salt	After thiazide	After salt	After salt	After thiazide	After salt
H. F.	203/112	191/102*	216/114	−2.4	+2.4	+158	−417	− 86
I. F.	198/104	179/ 94*	181/ 98	−1.5	+1.4	+301	−427	−211
M. F.	220/113	201/104*	223/101	−2.3	+1.2	+ 97	−409	−250
M. K.	173/105	150/ 97*	172/101	−1.3	+1.1	+334	−499	− 40
S. G.	205/115	176/103*	194/110	−0.5	+0.7	+253	−273	− 53
P. G.	209/118	196/108*	214/116	−3.4	+1.3	+497		
I. R.	184/111	154/103*	171/107	−0.3	+0.5			
J. A.	186/103	154/ 92*	190/104	−0.9	+0.9	+231		
R. R.	196/101	169/ 92*	175/ 97	−1.4	+1.1			
P. G.	179/112	146/ 94†	179/110	−1.8	+1.4	+320		
Mean†	197/109	174/ 99	193/105	−1.6	+1.2	+267	−405	−128
Mean change‡		−23/−10	+19/+6	−1.6	+1.2	+267	−405	−128
Standard deviation		7/1	10/5	.99	.5	130	82	96
p		<.001/<.001	<.001/<.01	< .01	< .001	<.01	<.001	<.05

*Hydrochlorothiazide in daily doses of 150 mg.

†Chlorothiazide in daily doses of 1.5 Gm. during long-term administration of reserpine.

‡Observations in patient P.G. during chlorothiazide were not included in calculations of the mean values.

cellular space. By extrapolation, the decrease of body potassium was derived largely from intracellular fluid.

Effects of Two Dosage Levels of Added Salt

After 4 weeks of administration of hydrochlorothiazide in daily doses of 150 mg., blood pressure and body weight were reduced in each of nine hypertensive subjects (table 2). The addition of 20 Gm. of sodium chloride daily for 2 weeks was attended by return of blood pressure and body weight approximately to control levels. Average blood pressure fell from 197/109 to 174/99 mm. Hg during the diuretic ($p<.001$) and rose to 193/105 mm. Hg during the addition of the salt load ($p<.001$). Body weight, which had decreased an average of 1.6 ± .99 Kg. ($p<.01$) during hydrochlorothiazide, increased an average of 1.2 ± .5 Kg. ($p<.01$) when the salt was added. The average 24-hour urinary excretion of sodium was 267 mEq. greater ($p<.001$) on the last day of the salt load than it had been before the addition of salt.

Twenty-four-hour exchangeable potassium decreased during hydrochlorothiazide administration in each of five subjects studied and remained low after the addition of salt (table 2). The large salt load further reduced body potassium, the average 24-hour exchangeable potassium falling an additional 128 ± 96 mEq. ($p<.05$).

In one subject 20 Gm. of sodium chloride were given daily for a week in the third month of administration of chlorothiazide. Blood pressure and body weight returned approximately to control levels (table 2).

The effects of the addition of 6 to 12 Gm. of salt daily for 1 to 12 weeks were examined in 10 hypertensive subjects during continued chlorothiazide therapy (table 3). These patients had taken chlorothiazide in doses of 0.75 to 1.5 Gm. daily for 1.5 to 7 months (average 4.0 months). The blood pressure, which had fallen from an average of 184/100 to 147/86 mm. Hg ($p<.001$) during administration of the diuretic, remained at the lower levels (average 148/84 mm. Hg) during this salt load. Body weight decreased 1 Kg. ($p<.01$) during chlorothiazide and in the group as a whole did not rise significantly when 6 to 12 Gm. of salt were added daily.

Table 3

Effects of the Addition of Six to Twelve Grams of Sodium Chloride Daily during Continuous Administration of Chlorothiazide

Patient	Daily dose of salt Gm.	Duration of addition of salt Wk.	Blood pressure mm. Hg			Weight change Kg.	
			Before chlorothiazide	After chlorothiazide	After salt	After chlorothiazide	After salt
J. S.	8	1	210/102	168/74	159/75	−0.1	±0.0
H. F.	8	3	194/133	185/118	182/116	−1.0	+0.5
I. F.	8	2	188/104	146/99	167/93	−1.3	+1.8
C. J.*	8	8	172/100	118/70	119/76	−1.0	−0.5
G. M.*	8	1	192/98	144/84	141/76	−2.0	−0.1
S. G.*	8	12	176/99	140/85	138/89	+0.6	−0.8
C. M.*	8	3	178/90	145/82	151/74	−0.8	+0.8
H. A.*	6	4	148/90	121/81	129/76	−1.6	+0.2
F. B.*	12	6	212/102	147/85	137/84	−0.3	+1.0
R. R.*	8	6	174/85	159/85	159/82	−2.1	+0.5
Mean			184/100	147/86	148/84	−1.0	+0.3
Mean change				−37/−14	+1/−2	−1.0	+0.3
Standard deviation				17/9	9/5	.9	.8
p				$<.001/<.001$	$>.1/>.1$	$< .01$	$> .1$

*During long-term reserpine therapy.

Three patients, however, had a gain in weight of approximately 1 Kg.

Effects of Repletion of Plasma Volume

Plasma volume was re-expanded by intravenous administration of 500 ml. of 6 per cent Dextran in 5 per cent glucose in water in 10 hypertensive subjects who had been treated with chlorothiazide or hydrochlorothiazide daily for 2 weeks to 9 months (average 2.5 months) (table 4). Each patient was given 500 ml. of 6 per cent Dextran in 5 per cent glucose in water intravenously at a rate of approximately 20 ml. per minute. Within 90 minutes plasma volume increased an average of 395 ± 231 ml. ($p<.001$). The hematocrit value fell an average of 4.2 ± 1.5 per cent ($p<.001$). Plasma volume was slightly overexpanded (mean + 161 ± 135 ml., $p<.05$) when compared in six cases with control values, an observation corroborated by the inverse changes in hematocrit level (table 4).

Systolic blood pressure rose but did not reach control levels when plasma volume was re-expanded (table 4). Diastolic pressure was unaffected. Blood pressure fell from an average of 191/111 to 159/91 mm. Hg during the diuretic ($p<.001$). After Dextran the blood pressure averaged 168/93 mm. Hg. The increase in systolic pressure was statistically significant ($p<.01$).

Discussion

Body sodium, potassium, and plasma volume are not increased in uncomplicated hypertensive disease.[14–18] Nonetheless, the reduction of blood pressure associated with the administration of chlorothiazide in nonedematous hypertensive subjects coincides with the increased urinary excretion of sodium, potassium, and water. The saluresis is essentially complete in 48 hours.[4, 6, 19] Extracellular fluid volume and plasma volume decrease promptly.

The source of the excreted sodium appears to be the extracellular fluid. The decreases in body weight, extracellular fluid volume, and 24-hour exchangeable sodium in the present studies after 6 to 8 weeks of chlorothiazide therapy are consistent with the loss of approximately a liter of isotonic extracellular fluid. These observations, in agreement with others,[6] do not suggest a loss of sodium or water from the intracellular space.

A fundamental relationship between the salt loss and the antihypertensive action of benzothiadiazines is indicated by the return of body weight and blood pressure approximately

Table 4

Effects of Intravenous Infusion of Dextran

Patient	Diuretic*	Duration of treatment wk.	Blood pressure mm. Hg. Before diuretic	After diuretic	After Dextran	Plasma volume ml. Change After diuretic	After Dextran	Hematocrit % Change After diuretic	After Dextran
I. F.	Hydro	36	188/102	150/87	160/88	−201	+241	+4.7	−3.5
P. G.	Hydro	2	211/123	187/105	205/102	−487	+771	−1.6	−3.3
J. S.	Hydro	24	210/102	167/77	175/73	+ 48	+326	−0.6	−4.4
I. F.	Hydro	2	210/112	172/91	180/98	−507	+586	+0.2	−2.5
H. P.	Chloro	10	216/114	151/84	155/85	−107	+199	−0.3	−5.2
H. F.†	Hydro	2	182/132	189/106	189/102	−454	+552	+3.0	−2.9
H. A.†	Chloro	3	160/110	134/86	137/89				
L. P.†	Chloro	4	180/100	151/94	153/95				
P. G.†	Chloro	6	180/112	143/93	165/97				
S. G.†	Chloro	8	176/99	149/85	163/96				
Mean		10	191/111	159/91	168/93				
Mean change				−32/−20	+9/+2	−285	+446	+0.9	−3.6
Standard deviation				18/7	7/5	219	252	2.4	1.1
p				<.001/<.001	<.01/>.1	<.05	<.01	> .1	< .001

*Diuretic: Hydro = hydrochlorothiazide 150 mg. daily.
Chloro = chlorothiazide .75 to 1.5 Gm. daily.

†During long-term administration of reserpine in doses of .25 to 1.0 mg. daily.

to control levels after the addition of 20 Gm. of sodium chloride daily during hydrochlorothiazide or chlorothiazide therapy. The efficiency of chlorothiazide as a saluretic agent was demonstrated by the observation that the addition of 8 Gm. of sodium chloride daily did not usually restore body weight to control levels, and in this study did not oppose the antihypertensive effect. Salt loads of 11 to 20 Gm. daily were found by others[20] to reverse the effects of chlorothiazide.

The deficit of potassium in the absence of a sodium deficit does not have a role in the antihypertensive action of benzothiadiazines. When the blood pressure was returned to the original hypertensive levels by the addition of 20 Gm. of salt daily, 24-hour exchangeable potassium remained low. Indeed, potassium was further depleted by the salt load ($p<.05$), a finding consistent with increased exchange of sodium and potassium at the distal tubule in response to an increased filtered load of sodium. Potassium was lost from both extracellular and intracellular fluid.

Plasma volume is reduced as much as 30 per cent in the first week of administration of chlorothiazide.[20] The degree of oligemia lessens in the course of several months. The reduction in plasma volume averaged 6 per cent after 2 months of continuous diuretic therapy in the present study ($p<.05$) and was insignificant after 6 months in another study.[6] Right heart pressure and cardiac output were reduced and peripheral vascular resistance increased in the first few weeks in several studies[21-23] but not in the study of Aleksandrow et al.[19] After 1 month of chlorothiazide therapy, peripheral vascular resistance was decreased.[24]

Oligemia and reduced cardiac output will exaggerate the effects of other drugs or pathophysiologic states influencing venous return, cardiac output, or vascular capacity. The hypotensive effects of ganglion-blocking agents, sympathectomy, and nitrites are increased by benzothiadiazines.[2-4, 20, 22, 25-28] Dustan et al. have suggested that oligemia enhances neurogenic vasomotor tone, fostering increased responsiveness to ganglioplegic agents.[22]

Wilson and Freis[6] found that during treatment with chlorothiazide, restoration of plasma volume by Dextran in saline or by Dextran in glucose in water returned blood pressure to pretreatment levels. In the present studies,

although plasma volume was slightly overexpanded by Dextran, systolic blood pressure rose but did not reach control levels, and diastolic pressure remained at the lower levels induced by the diuretic.

Substantiating the latter results are studies of the pressor responses to norepinephrine and the depressor responses to trimethapan and erythrol tetranitrate before and after continuous hydrochlorothiazide therapy, after intravenous infusion of Dextran and after the addition of 20 Gm. of salt daily: plasma volume repletion by Dextran diminished the effects of the diuretic on systolic responses to the vasoactive substances but had little effect on the diastolic responses; the addition of salt reverted these responses to control levels.[27, 28] Physiologic studies have demonstrated that changes in circulating volume or cardiac output exert a greater effect on systolic than on diastolic pressure.[29]

Although reduced plasma volume flow favors a fall in blood pressure, the baroreceptor reflexes oppose this effect. Chlorothiazide does not lower the blood pressure in normotensive patients. Hypertensive patients may have defective compensatory mechanisms, but another action of sodium depletion may exaggerate the effects of oligemia. The accumulated observations indicate that oligemia plays a role early in the antihypertensive action of benzothiadiazines but that salt loss must involve another mechanism by which peripheral vascular resistance is reduced.

Arteriolar muscular contractility may be impaired by altered relationships between extracellular and intracellular sodium. In vitro, changes in sodium gradient across cell membranes affect contractility.[30] Mendlowitz et al. observed a decrease in digital vascular reactivity to *l*-norepinephrine in hypertensive subjects during chlorothiazide therapy.[31]

In conflict with the thesis that sodium loss affects the sodium gradient and interferes with arteriolar contractility are the following observations. 1. The loss of sodium after benzothiadiazines appears to be isotonic and extracellular. 2. Although the absolute blood pressures during infusions of norepinephrine[32–35] or hypertension[36] are lower during administration of a diuretic than in a control period, the relative increments are equal or greater,[28, 36] suggesting that the ability of the arteriolar bed to respond to pressor substances is not reduced by sodium loss.

A reduction in tissue pressure or a decrease in arteriolar wall thickness may contribute to the antihypertensive effect of chlorothiazide. Tobian and Binion suggested that arteriolar walls are "water-logged" in hypertensive states.[37] Body sodium has, however, been found within normal limits in uncomplicated hypertension.[14–17] Extracellular fluid volume was elevated in some studies of experimental and human hypertension,[38–41] but not in others.[14, 42, 43]

Salt depletion may impair the function of a humoral or neurogenic pressor system. Hollander et al. were unable to demonstrate a decrease in renin during diuretic therapy.[4] Further studies of possible interrelationships between sodium depletion and pressor systems are indicated. The incomplete blocking of the antihypertensive effects of benzothiadiazines by restoration of plasma volume, the studies suggesting maintenance of the ability of the arteriolar bed to respond to pressor substances, and the decrease in peripheral vascular resistance observed after 4 weeks of therapy would be explained by such a mechanism.

A direct effect of benzothiadiazines on the central nervous system or the peripheral vessels appears unlikely in view of the fact that salt repletion returns both basal blood pressures and the responses to vasoactive substances to control values.

Summary and Conclusions

Blood pressure, body weight, extracellular fluid and plasma volumes, 24-hour exchangeable sodium and potassium, and serum potassium were reduced after 6 to 8 weeks of administration of chlorothiazide in 20 nonedematous hypertensive subjects. The loss of weight, water, and sodium approximated the loss of a liter of isotonic extracellular fluid.

The addition of 20 Gm. of salt daily to

hydrochlorothiazide therapy in nine patients and chlorothiazide therapy in one patient returned body weight and blood pressure to pretreatment levels, but further lowered 24-hour exchangeable potassium. The addition of 8 Gm. of salt daily usually failed to restore body weight to control levels and did not oppose the antihypertensive effects of chlorothiazide.

Expansion of plasma volume by Dextran to levels slightly above pretreatment values was associated with (1) a rise in systolic blood pressure but not to control levels and (2) no significant change in diastolic levels in 10 patients during administration of benzothiadiazine.

The antihypertensive effects of benzothiadiazines are due to sodium depletion and are not related to potassium loss. At least two mechanisms of antihypertensive action must be involved, one related to the effects of oligemia, and another possibly to an impairment of the function of a humoral or neurogenic pressor system.

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Observe, record, tabulate, communicate. Use your five senses.—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 99.

Biochemical Studies in Full-Blooded Navajo Indians

II. Lipids and Lipoproteins

By ROBERT J. KOSITCHEK, M.D., MOSES WURM, M.S., AND REUBEN STRAUS, M.D.

IT IS well known that distinctive ethnic groups display remarkably low incidence of coronary artery disease.[1-12] Implicit in many of these studies is the concept that such groups of individuals are protected against coronary artery disease by some genetic influence. This genetic explanation of immunity to coronary heart disease has been refuted in some instances by transposition of these individuals from their native to a Caucasian dietary environment.

The Navajo Indian "subsisting on a typical American diet,"[13] however, would appear to be an exception. It has been suggested that elevated serum gamma globulins as well as racial differences possibly could account for the low incidence of coronary artery disease and the low blood lipid levels in this group.[7] Since it has been shown that a correlation with respect to gamma globulin was not tenable,[14] it was considered advisable to study the lipid composition of the blood serum of the Navajo Indian.

Materials and Methods

The present study is based upon data secured from serum lipid analysis of 30 full-blooded Navajo Indians. Blood specimens were secured in 2 batches by personal visits to the Indian Reservation in the vicinity of Fort Defiance, Arizona, and from inmates of a detention installation in Shiprock, New Mexico. Except in 3 instances in which blood samples were knowingly collected postprandially, the remaining 27 were drawn as overnight fasting specimens. Eleven of these were secured under controlled conditions from prisoners in the stockade at Shiprock and the remainder were determined to be in a fasting state by intensive interrogation. Insofar as possible, the volunteers were selected as individuals having the least possible contact with local community life at the trading post, thereby attempting to exclude the influence of white contacts.

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All blood specimens were maintained under refrigeration, and analyses were begun within 24 hours. The analytical procedures for the determination of the various lipid and lipoprotein components were previously described.[15, 16]

Eighteen of the sample population were male and 12 were female. The individuals ranged in age between 25 and 75 years, with a mean of 48 years. All except 5 appeared normal. The exceptions were volunteers who appeared at the Fort Defiance Hospital as out-patients for minor ailments unrelated to cardiovascular disease. All volunteers were interrogated also concerning present or past complaints, particularly relating to pulmonary or liver disease.

The results of this study are compared with those of 3 other population groups; patients with manifest atherosclerosis, "normal," i.e., those with no evidence of coronary artery disease, and tuberculous patients, who as a group are demonstrated to evidence a low incidence of coronary artery disease. The analytical data for these contrasting groups have been previously published.[13, 17]

Results

The result of analytical data from the lipid analyses and calculated ratios are presented in table 1. Attention is directed to the values reported for Bel, Tso, and Tom, which, from our experience, are considered relatively elevated. The blood serum of these 3 individuals, however, was noted to be visibly hyperlipemic; but this was not unexpected, since the blood was knowingly secured postprandially. The remainder of the population displayed consistently low lipid values. The mean values for each of the lipids in the entire population, including the 3 lipemic specimens, are consistently lower than those found for the contrasting populations previously studied. Comparisons are made on the basis of statistically calculated Fisher "t" values,[18] which are presented in table 2.

The cholesterol, C/P ratios, beta lipoprotein, and gamma lipoprotein and neutral fat fractions in the Navajo Indians have values significantly different at a high level of con-

Table 1

Serum Lipid Components of Navajo Indians

Navajo Indians			Chemical analyses					Lipoproteins separated by electrophoresis (Fat Red 7 B)						
Name	Sex	Age	Chol. Mg. %	Phospholip. Mg. %	C/P Ratio	Tot. Lip. Mg. %	Neut. Fat Mg. %	Lip. Alb. (%)	α-1 Lipo. (%)	α-2 Lipo. (%)	β Lipo. (%)	NF + γ Lipo. (%)	β/α Ratio	β/ LipA Ratio
PIN-C	F	50	145	203	0.71	653	305	27.1	8.3	14.6	18.8	31.2	0.38	0.69
TSO-Z (Lip)	M	73	250	353	0.71	1819	1219	7.4	2.0	3.4	42.3	44.9	3.31	5.72
EDS-S	M	56	234	308	0.76	1540	998	9.9	2.1	2.8	55.6	29.6	3.76	5.62
MAR-R	M	55	169	263	0.64	886	454	17.6	7.9	15.7	27.4	31.4	0.67	1.56
WIL-T	M	59	192	266	0.72	931	473	16.3	7.3	7.3	45.5	23.6	1.47	2.78
WOO-L	F	68	152	258	0.59	816	406	26.6	6.4	10.6	29.8	26.6	0.68	1.12
WOO-N	F	66	205	278	0.73	1120	637	18.4	5.1	8.2	37.7	30.6	1.19	2.04
FRA-N	F	67	134	188	0.71	609	287	20.4	8.2	14.3	30.6	26.5	0.72	1.50
CHE-S	M	66	197	237	0.83	861	427	15.4	4.4	7.7	45.1	27.4	1.64	2.93
BEG-M	F	64	178	237	0.75	956	541	26.3	5.3	5.3	43.8	19.3	1.19	1.67
TOM-G (Lip)	F	58	235	318	0.74	1493	940	7.2	2.6	4.0	32.2	54.0	2.33	4.47
KIN-J	M	58	200	290	0.69	1096	606	14.2	3.8	8.5	33.9	39.6	1.28	2.39
BEL-W (Lip)	M	46	199	296	0.67	1353	858	7.6	2.5	5.1	63.3	21.5	4.17	8.33
JOH-K	M	55	178	222	0.81	560	160	26.0	3.9	7.8	45.4	16.9	1.21	1.75
KIN-T	M	45	164	222	0.74	609	223	24.6	7.0	5.3	38.6	24.5	1.04	1.57
JOE-S	M	24	143	200	0.72	536	193	25.4	6.3	14.3	28.6	25.4	0.62	1.13
WIN-R	M	52	226	275	0.82	980	479	19.2	3.8	5.8	49.1	22.1	1.70	2.55
JUM-B	M	37	181	242	0.75	700	277	24.7	2.5	12.3	42.0	18.5	1.06	1.70
LEE-R	M	41	138	190	0.73	536	208	26.3	3.5	10.5	35.1	24.6	0.87	1.33
LEW-J	M	39	227	278	0.82	1029	524	20.0	6.2	9.2	44.6	20.0	1.26	2.23
SMI-W	M	30	181	217	0.83	816	418	20.0	6.3	8.7	42.5	22.5	1.21	2.13
JOH-R	M	25	233	325	0.72	1162	604	16.5	2.4	3.5	61.1	16.5	2.73	3.71
DAL-J	M	64	167	220	0.76	770	383	16.9	4.2	5.6	43.7	29.6	1.63	2.58
BIL-E	F	51	189	250	0.76	653	214	26.1	3.1	12.3	38.5	20.0	0.93	1.48
REI-G	F	58	215	295	0.73	956	446	18.6	3.9	3.9	56.6	17.0	2.14	3.04
SIS-J	F	75	160	210	0.76	676	306	25.0	5.8	9.6	48.1	11.5	1.19	1.92
SCH-A	F	49	141	197	0.72	581	243	24.4	2.4	7.3	46.3	19.6	1.35	1.90
HIL-M	F	49	140	187	0.75	513	186	21.2	6.1	15.2	30.3	27.3	0.71	1.43
YAZ-N	F	40	161	245	0.66	746	340	22.5	5.0	7.5	42.5	22.5	1.21	1.89
YAZ-D	M	36	181	255	0.71	700	264	29.5	3.3	6.6	37.7	22.9	0.96	1.28
N = 30 Standard mean		52	184	251	0.73	888	454	20.0	4.7	8.4	41.2	25.6	1.49	2.48
Deviation			32.4	43.6	0.055	321	258	6.16	1.96	3.74	9.88	8.54	0.91	1.60

fidence from our contrasting populations of "normal," atherosclerotic, and tuberculous patients. While a highly significant difference is noted also for the phospholipids when compared to "normal" and atherosclerotic subjects, this appears not to hold when the Navajo Indians are compared to the tuberculous population. In fact, the extremely low Fisher "t" value 0.22, is considered by us to imply an identity for the two groups. With respect to all the other fractions, the mean values found for the Indian population and for the "normal" and tuberculous groups are not considered to be significantly different, since the indicated Fisher "t" values fall below 3.00. With the exception of the total lipids and alpha-1 lipoproteins, the greatest Fisher "t" values are found in all fractions when comparisons are made between the Indians and the group of atherosclerotic subjects.

Electrophoretic analyses of serum proteins performed on random specimens of the present sample of full-blooded adult Navajo Indians were found to be essentially similar to data secured in a previous study.[14]

Table 2

Fisher "t" Values of Serum Lipid Components of Navajo Indians Compared to Those of Three Control Populations

	N	A	T
Cholesterol:	6.03	7.48	4.90
Phospholipid:	3.60	3.81	0.22
C/P ratio:	6.00	9.50	14.0
Total lipid:	0.81	2.02	1.76
Lipalbumin (LA):	0.41	5.28	2.00
α 1 Lipoprotein:	0.10	2.09	1.96
α 2 Lipoprotein:	1.67	4.46	1.05
β Lipoprotein	4.87	9.30	3.80
Neutral Fat + γ lipoprotein:	5.87	5.37	3.89
β/α ratio:	1.60	5.96	1.05
β/LA ratio:	1.50	5.29	2.15

N = "Normal" individuals
A = Patients with coronary artery disease
T = Tuberculous patients

$$\text{"t"} = \frac{M_{IND} - Mx}{\sqrt{S.E._{IND}^2 + S.E._x^2}}$$

Discussion

The many published reports describing the low incidence of coronary artery disease in Bantus,[19] Australian aborigines,[9] Eskimos,[10,11] Aleuts,[2] Yemenites,[1] Peruvians,[7] Japanese and Hawaiians,[5,20] and Pima Indians[4] have left the impression that some racial factors are associated with this phenomenon. Keys[5,21] and others,[22,23] on the other hand, have demonstrated that in most instances their apparent immunity against coronary disease is probably causally related to the dietary intake of fats, as well as to the level of physical activity.[8] It has been reported that the Navajo Indian subsists on a "usual American diet" and exhibits practically no coronary artery disease.[13] Keys, however, reports 8 cases of arteriosclerotic heart disease, 2 with myocardial infarctions. It is our impression that this disease is exceedingly rare. McDermott et al.[24] reported only 3 cases of ischemic heart disease in a 3-year period in a limited portion of the population. In personal communication, O'Kane[25] revealed 5 cases at the PHS Indian Hospital at Fort Defiance, Arizona, between July 1, 1957, and December 31, 1958. Two of these occurred in patients with hypertension, one of whom also had diabetes, one in a patient with hypercholesteremia, and the remaining 2 in persons without such related diseases. The ages of these patients varied from 46 to 77 years, and only one (with diabetes and hypertension) was female. We are in agreement, nevertheless, that the Navajos subsist on a relatively meager caloric but relatively high-fat and carbohydrate diet, usually only 2 meals per day, consisting of broiled or stewed mutton, bread dough fried in mutton fat, and coffee usually with sugar only. They display also a special affinity for sweet foods (candy and soda pop) whenever available. The quantity of food consumed is somewhat restricted by its availability, unique and limited preferences for particular types of food, and lack of economic means to secure it. The above diet, traditional for the Indian from the interior, is probably considerably different from that for the Indian in the vicinity of the Trading Post. A more detailed evaluation of dietary habits will be the subject of a future report.

Page et al.[26] evaluated the interplay of a number of factors believed to be involved in

Table 3

*Coefficients of Correlation between Serum Lipid Components in Four Experimental Populations**

		Phosph.	T.L.	LAlb.	α1	α2	β	NF + γ	β/α	β/LAlb.
Cholesterol	N	0.86	0.80	0.76	0.58	0.82	0.79	0.59	0.79	0.78
	A	0.91	0.77	0.73	0.73	0.71	0.58	0.74	0.61	0.62
	T	0.85	0.87	0.65	0.64	0.74	0.71	0.56	0.66	0.63
	I	0.93	0.86	0.73	0.80	0.83	0.77	0.70	0.76	0.67
Phospholipid	N		0.90	0.71	0.52	0.76	0.72	0.58	0.72	0.64
	A		0.78	0.75	0.78	0.76	0.68	0.77	0.72	0.67
	T		0.89	0.66	0.51	0.68	0.68	0.57	0.66	0.64
	I		0.92	0.77	0.81	0.81	0.78	0.76	0.80	0.72
Total lipid	N			0.72	0.56	0.73	0.77	0.57	0.80	0.70
	A			0.72	0.54	0.67	0.56	0.89	0.72	0.78
	T			0.64	0.54	0.71	0.69	0.55	0.68	0.65
	I			0.88	0.77	0.76	0.65	0.75	0.85	0.82
Lipalbumin	N				0.65	0.72	0.86	0.68	0.82	0.90
	A				0.74	0.78	0.84	0.78	0.87	0.92
	T				0.64	0.65	0.77	0.63	0.74	0.89
	I				0.76	0.72	0.71	0.78	0.84	0.86
α1	N					0.56	0.62	0.56	0.58	0.70
	A					0.78	0.74	0.63	0.76	0.67
	T					0.66	0.65	0.56	0.64	0.60
	I					0.91	0.84	0.67	0.82	0.77
α2	N						0.79	0.61	0.78	0.77
	A						0.79	0.73	0.83	0.72
	T						0.77	0.63	0.77	0.68
	I						0.85	0.60	0.82	0.73
β	N							0.75	0.92	0.91
	A							0.79	0.91	0.80
	T							0.64	0.86	0.83
	I							0.56	0.84	0.77
NF+γ	N								0.65	0.69
	A								0.83	0.84
	T								0.55	0.60
	I								0.60	0.58
β/α	N									0.93
	A									0.87
	T									0.89
	I									0.96

*N, normal (N=40); A, atherosclerosis (N=40); T, tuberculosis (N = 67), I, Navajo (N = 30); Phosph., phospholipids; T. L., total lipids; LAlb., lipalbumin.

atherogenesis. Their conclusions regarding the role of heredity are not definitive. More recently Epstein et al.[27] re-examined this aspect of the problem in a restricted American population, specifically with respect to genetic mechanisms that influence serum cholesterol levels. Analysis of their data and those taken from the literature provided no firm basis for accepting without reservation any of the currently proposed genetic models of hypercholesteremia. Brunner and Lobl[1] also indicated that race and heredity are not involved in lipid patterns and predisposition to atherosclerotic disease.

It is our impression also that the general absence of coronary artery disease in the Navajo Indian is little, if at all, related to genetic influences but more likely to dietary habits. In the light of our experience with a tuberculous white population[17] and the well-known high incidence of tuberculosis in the Navajo Indian, it is also possible that this disease may contribute to the low incidence of coronary atherosclerosis. Additionally we should consider the possible influence of liver disease,[28, 29] although direct evidence for this in the Navajos is as yet unavailable.

The data presented in table 2 emphasizes significantly different mean lipid values and calculated ratios for the Navajo Indians correlated with the 3 other population groups. These results, especially the beta/alpha ratio,

support the observations that the incidence of coronary artery disease is indeed minimal in the Navajo Indian.

Nichols et al.[30] reported that the atherogenic index determined by ultracentrifugation correlates considerably better with the serum total lipids than with cholesterol. In table 3 we have collected the coefficients of correlation between each of the lipid fractions in the 4 experimental population groups. From this it would seem that our beta/alpha and beta/lipalbumin ratios (atherogenic indices) also correlate slightly better with the total lipids than with cholesterol, but the difference is so small and the values for the coefficients of correlation so low and variable that the relationship seems not to be significant.

It is noteworthy that in some instances all 4 population groups show very similar values. For example, the coefficient of correlation is uniformly high for the beta/alpha and beta/lipalbumin ratios on the one hand and the lipalbumins and beta lipoprotein on the other. Similar values are secured for the total lipids, cholesterol, and phospholipids. Such correlation may imply that the biochemical mechanism for handling these specific lipids, at least, is the same for each of the groups. In most instances, however, the coefficients of correlation are low and variable, suggesting a random relationship. In some instances the coefficient of correlation of some lipids appears to be strikingly and consistently different in 1 population group contrasted with the other 3, such as the low value of the beta lipoprotein-cholesterol coefficient in the atherosclerotic population or the high value between lipalbumin and alpha-1 lipoprotein on the one hand correlated with the total lipid on the other for the Navajo Indian population.

From the data presently at hand, it would be premature to suggest that different metabolic capabilities, perhaps in part, are genetically available to the Navajo Indian. On the other hand, it should be stressed that the dietary habits of this ethnic group are unique and probably contribute significantly to the blood lipid picture. Our data, particularly with respect to lipoproteins, provide objective evidence to support the low incidence of coronary heart disease in the Navajo Indian.

Summary

The beta/alpha lipoprotein ratio and other serum lipid components have been studied in a population of full-blooded Navajo Indians. The findings offer a basis for assessing the low degree of atherogenesis and are consistent with evidence for the low incidence of coronary heart disease in this ethnic group.

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The investigator should not only possess but also train himself in keen powers of observation. He should be alert and watchful as events transpire in the course of experiments, so that nothing escapes his vigilance. We readily behold the familiar; we may overlook the unfamiliar. An old saying has it: 'We are prone to see what lies behind our eyes rather than what appears before them.'—WALTER B. CANNON, M.D. *The Way of an Investigator*. New York, W. W. Norton & Co., Inc., 1945, p. 36.

The Electrocardiogram in Ventricular Septal Defect

By DENNIS J. VINCE, M.D., AND JOHN D. KEITH, M.D.

THE PROGNOSIS and indications for treatment in children with ventricular septal defects are dependent on three fundamental factors: the size of the defect, the amount of blood flowing through it, and the response of the pulmonary vasculature to the increased blood flow. The electrocardiogram has proved a useful tool in estimating the severity of these factors by giving some indication of the dynamics in any individual case.

To assess this in detail, we have studied 119 cases of isolated ventricular septal defects with intracardiac catheterization and electrocardiogram, oximetry, and fluoroscopic and physical examination. They all had repeated electrocardiograms over months or years, and in a number of cases the cardiac catheterizations were repeated. The 12 commonly used electrocardiographic leads were obtained, including precordial leads V_{3R} to V_6. In many instances, additional leads to right or left were also recorded.

Since this study was begun, several articles have appeared in the literature on the electrocardiogram in ventricular septal defect.[1-11] There is general agreement on the presence of various patterns of systolic and diastolic loading, but the incidence of these patterns and their significance for the dynamics of the heart have met with a difference of opinion. We have therefore presented our own criteria, primarily in the identification of right and left ventricular loading. At the end of the study additional criteria have been set down to aid in the recognition of the hemodynamics of the pulmonary circulation in an infant or child with a ventricular septal defect.

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Criteria for Identification of Ventricular Loading Patterns

The electrocardiograms taken at the time of cardiac catheterization were reviewed and divided into four patterns, normal, left ventricular loading, combined ventricular loading, and right ventricular loading, according to the criteria in table 1.

It was decided not to use the axis as a criterion for right or left ventricular loading in this study, but to note how the axis related to other criteria. Notching of the P wave and late inversion in V_1 with broadening of the P wave will be referred to in the discussion as will the counterclockwise vector.

Results

A general summary of our findings is shown in table 2, which reveals that normal electrocardiographic patterns appeared in 14 per cent of the cases, left ventricular loading in 11 per cent, combined ventricular loading in 61 per cent, and right ventricular loading in 14 per cent. As might be expected, the majority of the cases fell into the group that had combined ventricular hypertrophy.

The normal pattern and the combined ventricular pattern were approximately equally divided between the cases over and under 1 year of age. The right and left ventricular loading patterns were much more commonly found after 1 year of age than under 1 year. This is to be expected, since the right ventricle is physiologically approximately equal to the left ventricle at the time of birth, and the dominance of one ventricle over the other usually requires many months or years to develop.

Details of Patterns

The P-R interval was 0.18 second or longer in 6 per cent of the cases. The average was that usually found in normal children. The P-wave duration was found to be slightly prolonged in 30 per cent of the cases (fig. 1).

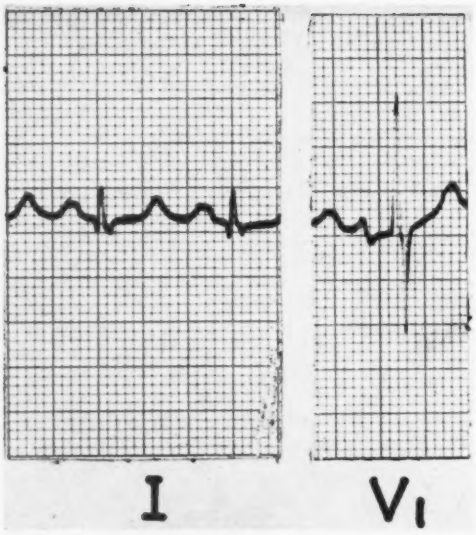

Figure 1

Standard lead I shows broadening and slight notching of P wave. It is accompanied by late inversion of P wave in precordial lead V_1.

The height of the P waves was within normal limits. Significant notching of P in leads I or II was noted in more than one third of the cases (table 3).

Notching and broadening were found almost entirely in groups with either left or combined loading and within these groups this sign was accompanied by a tall R or a deep Q in nearly every instance. It appeared therefore to offer good additional evidence of diastolic loading of the left atrium and left ventricle.

The axis varied from −20 to +150 in the normal group, from −20 to +90 in the left ventricular hypertrophy, from −170 to +90 in in the right ventricular group, and from −75 in a clockwise direction to −170 in the combined hypertrophy group. Only 3 cases had an axis between −30 and −90 (fig. 2). All with axis less than 90° had a tall R or deep Q in V_6, or deep S in V_1, or notching and broadening of the P wave.

As would be expected, the direction of the vector followed the direction of the axis as a general rule. The number of cases with clockwise and counterclockwise vectors are shown in table 4. Approximately one third had a counterclockwise vector and 80 per cent of these had an axis less than 90°. There were 26 such cases, and all had other evidence of a relatively low pulmonary vascular resistance and good pulmonary blood flow. All but 2 satisfied the criteria of DuShane et al.;[12] they had other evidence of satisfactory pulmonary blood flow. Among the cases with counterclockwise vector and an axis of 90° or over, all satisfied the criteria of DuShane et al. for operability.

The height of the T wave in V_6 was somewhat elevated in 5 per cent of cases (over 4 mm. under 1 year, over 5 mm. over 1 year).

In the children over 1 year of age the average height of the T wave in V_6 was essentially the same in all 4 groups, averaging 3.1 mm. in the normal, 2.1 in those with left hypertrophy, 3.0 in those with combined hypertrophy, and 3.0 in those with right ventricular hypertrophy. The T wave tended to be slightly lower in the children under 1 year of age, averaging in the normal 2.3 mm., in the left hypertrophy group 3.1, the combined hypertrophy group 1.7, and the right ventricular hypertrophy group 1.7. The height of the T wave in V_6 did not significantly aid in defining diastolic loading of the left ventricle (table 5).

DuShane et al.[12] have paid a good deal of attention to the height and peaking of the T wave in leads II, III, or aV_F. They have stated that a tall peaked T wave in these leads is indication of a sufficiently low pulmonary vascular resistance to permit successful surgery on the ventricular septal defect. They do not specify how tall the T wave needs to be. In our series a T wave of 4 mm. or more included a number of cases that had markedly increased pulmonary vascular resistance and reversal of flow. This was also true of 5 mm. or more. It was also true if 4 mm. or more in all 3 leads were taken as a basic criterion. The peaking appeared to be a function of the height.

Tall T waves in many cases appeared to be related to deep wide S waves, which were associated with right bundle-branch block or right ventricular loading and did not in any

Table 1

Criteria of Loading Patterns*

Right ventricular loading
1. Voltage of R in V_1 greater than maximum normal for age.
2. Voltage of S in V_6 greater than maximum normal for age.
3. R/S ratio in V_1 greater than maximum normal for age.
4. Positive T in V_1 after third day of life when R/S ratio greater than 1.0.
5. qR pattern in V_1.

Left ventricular loading
1. Voltage of R in V_6 greater than maximum normal for age.
2. Voltage of S in V_1 greater than maximum normal for age.
3. R/S ratio in V_1 less than minimum normal for age.
4. Secondary T inversion in V_5 and/or V_6.
5. Deep Q over the left precordium—4 mm. or greater.

Combined ventricular loading
1. Direct signs of right plus left ventricular loading (as above).
2. Direct signs of right ventricular hypertrophy with the following signs in the left chest leads:
   (a) q wave (1 mm. or more).
   (b) T_6 inversion, after a positive T in right chest leads.

*The term loading has been used rather than hypertrophy, since it is a broader term, and hypertrophy may or may not be present.

way resemble the R and Q changes characteristic of diastolic loading of the left ventricle. A tall T in these particular leads is also dependent on the axis of T being +120 and +60°.

The most common characteristic feature of QRS patterns in V_1 is a relatively large R and S (table 6). With or without an original small R and S it occurred in 87 per cent. This is to be expected, since there is usually increased activity of both ventricles. The right bundle-branch block pattern of R′ is a common finding in congenital heart defects with increased diastolic loading of the right ventricle, and was present in 40 per cent of our cases.

There were no instances of a QR pattern in V_1, although it was occasionally seen in RV_3 or leads farther to the right. This is usually associated with systolic or diastolic overloading of RV and frequently is accompanied by an enlarged right atrium. Such a picture does not occur in the isolated ventricular septal defect in childhood in our experience.

Two cases showed a qRs pattern in V_1, and both were associated with enlarged hearts and a pressure in the right ventricle at systemic level.

A Q wave in V_6 was considered most significant, if it was 2 mm. or more; such was the case in 60 per cent. In 40 per cent it was 3 mm. or more. There is good evidence that this implies an active left ventricle with diastolic loading and correlates with the hemodynamic data in ventricular septal defect. A Q_6 of 1 or 2 mm. is of more significance in this regard when associated with evidence of right ventricular loading (table 7).

Pulmonary Blood Flow

The electrocardiographic patterns helped considerably in separating the various groups in relation to pulmonary blood flow (table 8). When the electrocardiogram was normal, the flow was invariably relatively low, never more than twice systemic whether the age group was over or under 1 year. When a left ventricular loading pattern was present, the flow through the pulmonary artery was usually not large but occasionally exceeded four times the systemic.

When a right ventricular loading pattern was found alone in the electrocardiogram, the pulmonary blood flow was not large, but in six cases was up to two or three times the systemic. In these cases there was no reversal

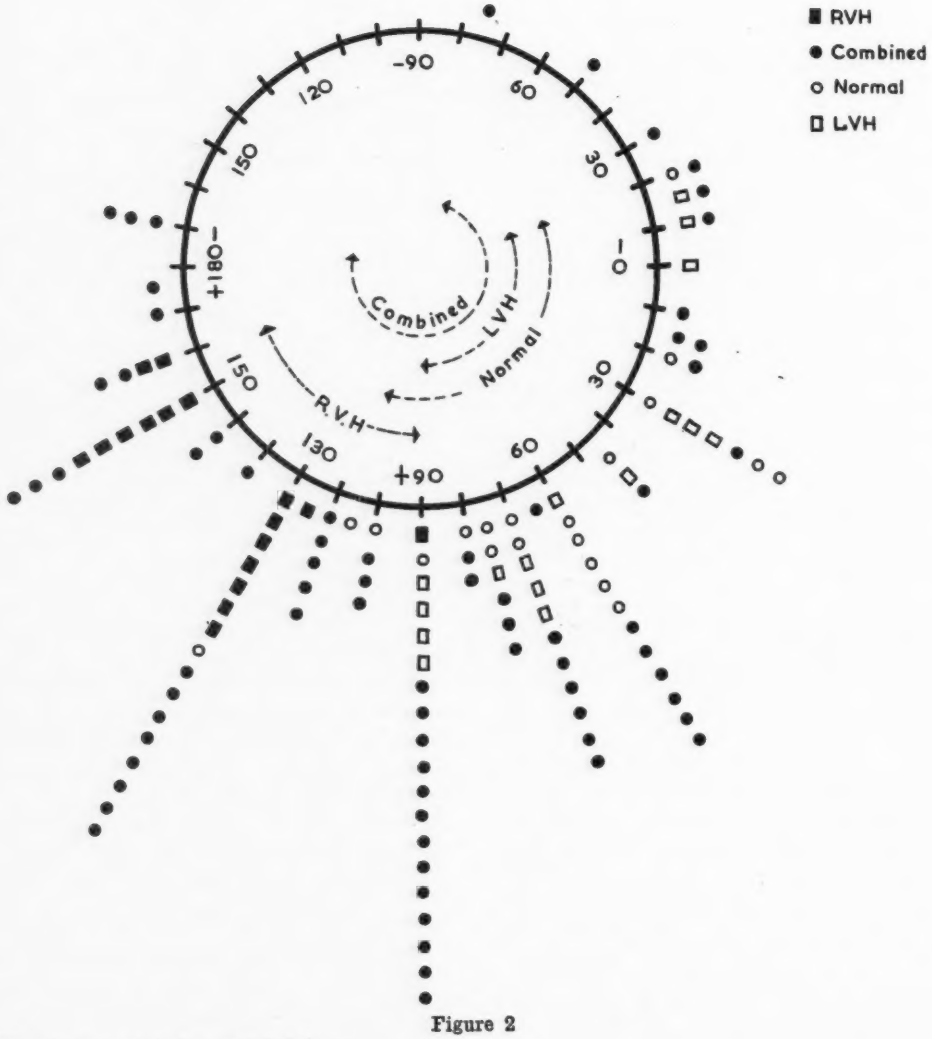

Figure 2

QRS axis in ventricular septal defect.

of flow with exercise, while in the seven cases that had a flow of only one or two times systemic, all had reversal of flow with exercise. The greatest flows and greatest variations were found in the combined loading group. In this group more of the younger children had larger flows than the older children, as one would expect. Reversal of flow in these cases occurred almost entirely among those with a large flow and systemic pressure in the pulmonary artery. The hemodynamic findings in the group suggested that the majority were likely to respond satisfactorily to surgery.

Correlation between the Pressure in the Right Ventricle and Electrocardiogram

Table 9 shows that there is some correlation between the pressure in the right ventricle and the electrocardiographic pattern. When a normal electrocardiographic pattern was present, the pressure in the right ventricle rarely

Table 2

*Ventricular Loading Patterns**

Electrocardiographic pattern	Age (yr.)	No. of cases	Per cent of total cases	Combined per cent
Normal	<1	7	5.9	14.3
	>1	10	8.4	
Left	<1	3	2.5	10.9
	>1	10	8.4	
Combined	<1	35	29.4	61.3
	>1	38	31.9	
Right	<1	2	1.7	13.5
	>1	14	11.8	

*Total number of cases 119; 39.5 per cent under 1 year, 60.5 per cent over 1 year.

Table 3

Notching of P Waves (Leads I and II)

Electrocardiographic pattern	Age (yr.)	No. with notching and broadening of P in lead I or II	Total cases reviewed
Normal	<1	1	7
	>1	1	10
Left ventricular loading	<1	1	3
	>1	6	10
Combined ventricular loading	<1	10	34
	>1	16	36
Right ventricular loading	<1	1	2
	>1	0	14
		36*	116

*There were 4 additional cases that showed broadening of P_2 and late inversion of P in V_1 but without notching.

exceeded 40 mm. Hg. When left ventricular hypertrophy was present, the majority had pressures in the right ventricle under 50 mm. Hg, and only rarely did it exceed 60 mm. Hg. The combined ventricular hypertrophy group showed the greatest variation, and again the pressures correlated with the predominant hypertrophy pattern; where it was predominantly right, it tended to be high.

When isolated right ventricular hypertrophy was present in the electrocardiograms, the pressure was rarely lower than 60 mm. Hg and was almost invariably at systemic level.

Oximetry

The information obtained by the ear oximeter correlated well with the electrocardiographic data. In table 10 are shown the results following exercise. When a normal or left ventricular hypertrophy pattern was present, none showed a drop in arterial oxygen saturation with exercise. When combined ventricular hypertrophy was found in the electrocardiogram, approximately 17 per cent had a drop with exercise, a similar percentage being present whether over or under 1 year of age. When a pattern of isolated right ventricular hypertrophy was found in the electrocardiogram, 60 per cent showed a drop in oxygen saturation. As might be expected, the percentage with reversal of blood flow through the ventricular septal defect during exercise was much higher in those with right ventricular overloading alone, since they were associated with high pulmonary vascular resistance in most cases. In a few instances in this latter group, the pulmonary vascular resistance we only moderately increased, and no drop in arterial oxygen saturation occurred following exercise. In those with combined hypertrophy in which the right hypertrophy was markedly predominant, reversal of flow through the defect was more likely. This would appear to be due to the combination of a large volume flow through the lungs and increased pulmonary vascular resistance.

Physical Findings

Normal Electrocardiographic Pattern

In this group a *loud, harsh murmur* and thrill were found in all; the cardiothoracic ratio varied between 52 and 68 per cent. The hilar shadows were increased and many were pulsating. The pulmonary second sound was increased slightly in about 30 per cent.

Left Ventricular Hypertrophy

A loud harsh murmur and thrill were present in all of these cases. In all, the pulmonary second sound appeared within normal limits, and intensity and normal splitting were noted. The cardiothoracic ratio varied between 50 and 69 per cent. Left atrial enlargement was demonstrated radiologically in 7 of the 10 children over 1 year of age.

Combined Ventricular Hypertrophy

All these cases had the usual murmur and thrill, approximately a quarter of those in

Table 4

Electrocardiographic Pattern and Direction of Vector Loop

Electrocardiographic pattern	Age (yr.)	Clockwise vector No. of cases	Counterclockwise vector No. of cases
Normal	<1	8	0
	>1	7	3 (—20, +30, +60)
Left ventricular loading	<1	3	2 (0°, +90°)
	>1	6	4 (—15, —10) (+20, +30)
Combined ventricular loading	<1	24	9 (—30, —160, +15, +45) (+70, 70, 70, +60)
	>1	25	13 (—10, —50, —75, +15) (+20, +30, +30, +70, +80) (+90, +90, +90, +150)
Right ventricular loading	<1	2	0
	>1	13	0

Table 5

Height of T Waves in Leads II, III, or aV_F

Electrocardiographic pattern	Age (yr.)	Total cases	T wave in any 1 lead 4 mm. or more	5 mm. or more	T wave in all 3 leads 4 mm. or more	5 mm. or more
Normal	<1	6	= 2	1 yr. = 2	1 yr. = 2	0
	>1	10	= 4	1 yr. = 3	1 yr. = 0	0
Left	<1	5	= 2	1 yr. = 1	1 yr. = 0	0
	>1	10	= 7	1 yr. = 4	1 yr. = 2	0
Combined	<1	40	= 24	1 yr. = 18	1 yr. = 5	4
	>1	30	= 14	1 yr. = 11	1 yr. = 13	8
Right	<1	2	= 1	1 yr. = 1	1 yr. = 1	0
	>1	14	= 12	1 yr. = 8	1 yr. = 5	0

the first year of life showed signs of failure at some time, and many of the others had dyspnea at rest. All had evidence of increased pulmonary flow on fluoroscopic examination, although pulsations in the hilar shadows during the first year were hard to see. The second sound was increased in approximately half of them, and the cardiothoracic ratio varied from 50 to 70 per cent.

Right Ventricular Hypertrophy

The systolic murmur was frequently short and occasionally absent in this group. The thrill was the exception rather than the rule. Clinical cyanosis was observed in 6 of the 16 cases at rest. A precordial lift to the right ventricle was present in all over 1 year of age. The pulmonary artery bulged under the fluoroscope, and hilar shadows were increased. Pulsation of the hilar shadows was evidenced in the majority. One child at the age of 12 showed only very questionable pulsations. The second sound was uniformly loud and closely split; in 1 case it appeared to be single. The and 82 per cent of these had an axis of less heart size was slightly smaller than in the combined ventricular hypertrophy group.

Changing Electrocardiographic Pattern

From repeated electrocardiograms in 61 cases table 11 was drawn up to show the relationship of the four fundamental patterns to change over the years of follow-up. The time in follow-up varied from 7 months to 7 years, and the average between the first and the last electrocardiogram was 3 years.

Among the cases that did not have isolated right ventricular systolic loading to begin with, only one developed this pattern later during the period of observation. Our first

Table 6

Summary of the QRS Patterns in Precordial Lead V_1

Number of cases	qR	qRs	rsR′	rsr′	rsR′S′	RS	R	rS
<1 year	0	2	3	2	10	30	0	0
>1 year	0	0	7	0	27	37	1	2

Table 7

Size of Q Wave in V_6

0	1 mm.	1 mm.	2 mm.	3 mm.	4 mm.	5 mm.	6 mm.	7 mm.	8 mm.	9 mm.	10 mm.
16%	4%	20%	15%	17.5%	11%	7%	2.5%	2.5%	2.5%	1%	1%

electrocardiogram was done at 4 months of age (fig. 3), and the last at 4 years. The combined ventricular loading was changed to pure right, with no evidence of left systolic or diastolic loading. Re-catheterization showed a relatively constant state over the childhood years. A gradual shift may occur from combined ventricular loading to isolated right. Those that have this latter pattern are chiefly in the age group from 6 to 13 years. Some of the cases with right loading showed deepening S in V_6 over a period of a few years.

It would appear that evidence of left ventricular loading in a child over 2 or 3 years of age, or an isolated right ventricular loading pattern, is likely to be maintained for long periods.

In a few cases with combined loading, the right ventricular loading pattern has become increasingly dominant after 1 or 2 years of age. The most characteristic pattern was that of left loading. Of the 61 cases followed over several years, 43 remained unchanged (most had left loading at first observation); 11 developed signs of left loading when it was not present before. The new appearance of right loading was an uncommon event, since most of our cases were followed from infancy during the early years. These findings indicate that the presence or appearance of left diastolic loading after the fetal pulmonary vascular pattern recedes is a common event.

Discussion

There have been numerous studies on the electrocardiogram in ventricular septal defect. Several authors have dealt with the incidence and criteria of right and left ventricular hypertrophy patterns in this defect. A distinct advance in our understanding of the relationship of the electrocardiogram to the underlying physiology was made by Sodi-Pallares and co-workers[13] when they outlined the criteria for systolic and diastolic loading of the heart chambers. The tall R in V_1 with inverted or upright T waves as evidence of right ventricular systolic overload has stood the test of time. The tall broad R waves, the lengthened ventricular activation time, and the flat or inverted T waves in V_6 are accepted as good evidence of left ventricular systolic overloading. The rsr pattern in V_1 not uncommonly occurred with right ventricular diastolic loading, but frequently occurred in normal patients also, and is, therefore, much less specific than those mentioned above. The tall peaked upright T waves in standard leads II, III, and aV_F and V_6 are of little value in indicating left ventricular diastolic overload except when accompanied by tall R waves or a deep Q in V_6. The latter criteria presented by Sodi-Pallares and co-workers[13] have needed more accurate definition, and this has been provided lately, to some degree, by DuShane and associates[12] in elucidating those cases with ventricular septal defect that show diastolic loading. Their criteria were as follows: a tall R in V_6, a deep S in V_1, a Q in V_6 of 4 mm. or greater, an axis of 0 degrees (or less than 60 when the age is under 3), a counterclockwise direction of the vector under the age of 3, and tall peaked T waves in leads II, III, or aV_F. They concluded that if any one of these criteria was present in patients undergoing

Table 8

Electrocardiographic Pattern and Ratio of Pulmonary to Systemic Blood Flow

Electrocardiographic pattern	Age (yr.)	Total cases	Ratio of pulmonary flow to systemic			
			1-2 times	2-3 times	3-4 times	4 times or over
Normal	<1	7	3	0	2	2
	>1	9	9	0		
Left loading	<1	3	2	0	0	1
	>1	10	5	3	1	1
Combined loading	<1	34	7	9	14	
	>1	35	11	4	10	
Right ventricular loading	<1	2	1	1	0	
	>1	13	7	6		

Table 9

Relationship of Right Ventricular Pressure to Electrocardiographic Loading Pattern

Electrocardiographic pattern	Age (yr.)	Right ventricular pressure mm. Hg (systolic)										
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	100-109
Normal	<1			5	1	0	1[50]					
	>1			6	3	1[40]						
Left	<1			1	1	1						
	>1		1	2	2	1	2	1	1			
Combined	<1		1	0	4	5	6	10	4	4	1	
	>1			1	5	3	7	7	6	3	4	2
Right	<1								1			1
	>1					1		2	0	3	4	4

surgery, 96 per cent showed a satisfactory drop in pressure in the pulmonary artery postoperatively. These are helpful criteria, but on reviewing our data we find that a number of important modifications are needed. These relate to the axis of QRS, the counterclockwise vector, the tall peaked T wave in leads II, III, and aV_F, and P-wave abnormalities such as notching, broadening in the standard leads, and late inversion in V_1.

Axis

We find the axis to have a broader and more applicable significance than was noted by DuShane's group.[12] Whenever the axis was less than 90° we found other evidence of a moderate or low pulmonary vascular resistance that would be expected to permit successful surgery. This axis occurred in approximately one half of our cases, appearing only in those that had an electrocardiographic pattern showing normal, left, or combined loading. It was not seen in those with a pure right loading configuration.

Counterclockwise Vector

As would be expected, the direction of the vector followed the direction of the axis as a rule. One third had a counterclockwise vector, and 82 per cent of these had an axis of less than 90°. Thus the axis is a more useful measurement than the direction of the vector. There were, however, 7 cases that had a counterclockwise vector with an axis 90° or more. On reviewing these separately it was obvious that they had other evidence of relatively good pulmonary blood flows and would, therefore, fall into the operative group.

Tall Peaked T Waves

DuShane and associates[12] have stated that a tall peaked T wave in standard leads II, or III, or in aV_F is indicative of sufficiently low pulmonary vascular resistance to permit successful surgery on the ventricular septal defect. They do not state how tall the T wave needs to be. If the T wave is 4 mm. or more, this includes a large number of cases that have marked pulmonary vascular resistance with

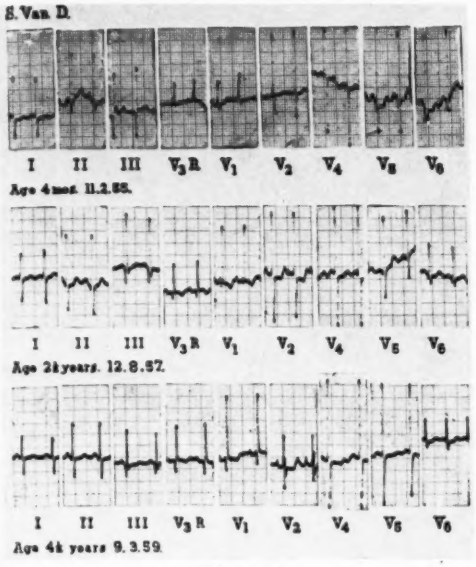
S. Van D.
I II III V3R V1 V2 V4 V5 V6
Age 4 mos. 11.2.58.
I II III V3R V1 V2 V4 V5 V6
Age 2½ years. 12.8.57.
I II III V3R V1 V2 V4 V5 V6
Age 4½ years 9.3.59.

Figure 3

Electrocardiogram at 4 months shows a tall R and deep Q in V_6. At 2½ years and at 4½ years one sees a diminishing R and Q in V_6, at the same time the R in V_1 is increasing in height. These findings are consistent with increasing pulmonary vascular resistance.

reversal of flow. If the measurements included only those 5 mm. or more, it still included a number of cases that should be eliminated. We have one case (a boy of 15 years) whose T wave in II is 9 mm., tall and peaked, whose oxygen saturation drops to 60 per cent with exercise, whose heart is not significantly enlarged, and whose hilar shadows are increased centrally, but cut off peripherally. The chances of successful surgery in him would appear slim. If only those with T waves in all 3 leads II, III, and aV_F of 4 mm. or more are accepted, the above-mentioned boy is eliminated; but an analysis of our cases indicates that several of those included by this measurement would be bad risks.

If only those with T waves of 5 mm. or more in all 3 leads II, III, and aV_F were included, there were usually other signs indicating operability: but again exceptions appeared.

The height of the T in II, III, and aV_F appears to be related to the direction of T vector and the area of the QRS complex. This

Table 10

Oximetric Studies

Electrocardiographic loading pattern	Age (yr.)	Total done	Number showing drop with exercise
Normal	<1	5	0
	>1	5	0
Left	<1	1	0
	>1	8	0
Combined	<1	28	5
	>1	23	4
Right	<1	1	1
	>1	14	8

is particularly misleading when a deep S wave occurs with or without right bundle-branch block. There is no constant relation to the pulmonary flow or diastolic loading of left ventricle. We cannot demonstrate any significant help in selecting cases for surgery by this method.

Char and associates,[8] studying surgically treated cases, found some correlation between the height of the T in V_6 and survival rate. The prognosis was better if the T in V_1 was inverted, and better if the T in V_6 was upright and tall. If the T in V_1 was upright and the T in V_6 down, the prognosis at the operation was poor, with survival of only 2 out of 10 cases.

Broad Notched P Waves

An analysis of the P wave in the electrocardiogram in the ventricular septal defect group is of interest, since it is associated with increased flow or pressure in the left atrium, and thus gives us another indication of pulmonary vascular resistance.

Dines and Parkin[14] have reviewed P wave morphology in patients with increased left atrial pressure and left atrial enlargement. They point out that notching and broadening of the P wave in standard lead I or II is the best evidence of this pathology. Broadening of the P wave and late inversion of the P in V_1, associated with broadening, are also evidence of the same pathology. In the pediatric age group a P wave over 0.09 second was taken as significant broadening. The broadening of the P wave is an important accompaniment of late inversion of the P wave in pre-

Table 11

Electrocardiographic Pattern

	Total	Remained unchanged	Became normal	Became left loading	Became combined loading	Became right loading
Normal	10	5	0	3	2	0
Left ventricular loading	6	6	0	0	0	0
Combined ventricular loading	34	25	5	3	0	1
Right ventricular loading	11	7	1	0	3	0

cordial lead V_1. Late inversion alone may occur in normal persons.

There appears to be no close relationship between the anatomic type of ventricular septal defect and the electrocardiogram, except that the smaller defects are associated with normal patterns or left loading and the larger ones with combined or pure right loading.

Toscano-Barboza and DuShane[10] suggested that when the electrocardiographic pattern of isolated left ventricular overload, such as seen in patent ductus, occurs in ventricular septal defect, it is associated with an opening between the right and left ventricles in the outflow tract of the right ventricle. On reviewing our electrocardiographic and pathologic material we were unable to substantiate this finding in any single case. Furthermore, on reviewing their paper, we note that one of their cases had such an electrocardiographic pattern and yet the ventricular septal defect was found at operation to be in the membranous portion of the septum.

The Q Wave in V_6

A special word is required regarding the Q wave in V_6. In a recent study Watson and Keith[15] demonstrated that 74 out of 95 cases of tetralogy of Fallot had a Q wave in V_6 of less than 1 mm. All these cases were associated with a high pulmonary vascular resistance in the sense that they had obstruction at the entrance to the pulmonary artery. The other 26 per cent that had a Q wave of 1 mm. of more were those that had associated patent ductus, a Blalock operation, or a relatively high oxygen saturation of the arterial blood at rest and with exercise. All this latter group had a good volume flow through the lungs returning to the left ventricle, averaging twice the systemic flow. The presence of this good pulmonary flow was suggested by a significant Q in V_6. These findings may be compared with those of our group of 119 cases of ventricular septal defect. Eighty per cent of our series had a Q wave in V_6 of 1 mm. or more, and again this appears to be clear evidence of a considerable diastolic volume flow to the left ventricle, since those that did not show this Q wave were either those that had high pulmonary vascular resistance with reversal of flow through the defect, or very mild cases with a normal electrocardiogram that had normal flows, and, therefore, no diastolic overloading of the left ventricle. In spite of the fact that a Q wave in V_6 may occur frequently in the normal, a review of this data indicates that a Q wave bears a close relationship to the presence or absence of a diastolic overloading in the ventricular septal defect group, especially when the electrocardiogram shows a systolic loading of the right ventricle at the same time. Twenty-five per cent of our cases with ventricular septal defect showed a Q wave in V_6 of 4 mm. or more, 60 per cent had a Q of 2 mm. or more. A Q wave of 4 mm. was always associated with other evidence of left diastolic loading, such as a tall R in V_6, or deep S in V_1, or notching of P wave, a left axis or a pulmonary blood flow more than two times systemic. The same could be said of a Q in V_6 of 2 mm. or more. There

Table 12

Electrocardiographic Criteria for Recognition of Low or Moderately Raised Pulmonary Vascular Resistance in Ventricular Septal Defect

Electrocardiographic pattern	Age (yr.)	Total cases	20 mm. or more tall R in V_6	4 mm. or more Q in V_6	Tall R_6 and deep Q_6	25 mm. or more deep S in V_1	R_1/S_1 ratio	Q in V_6 mm. 1-2	Q in V_6 mm. 2-4	Broadening and notching of P, lead I	Broad P and late inversion in V_1	Axis less than 90°	Counterclockwise vector	Pulmonary to systemic blood flow ratio <2 times	Pulmonary to systemic blood flow ratio >2 times	Reversal of flow	Age 6 years or under
Normal	<1	7	0	0	0	0	0	2	2	1	1	4	0	3	4	0	7
	>1	10	0	0	0	0	0	4	5	1	1	9	4	10	0	0	7
Left loading	<1	3	2	3	2	0	0	0	0	1	1	1	2	2	1	0	3
	>1	10	8	5	5	3	2	0	3	6	5	9	4	5	5	0	5
Combined loading	<1	34	16	12	7	9	2	12	5	10	7	16	14	6	28	6	34
	>1	36	16	12	7	4	1	7	15	16	16	18	13	11	25	3	29
Right loading	<1	2	0	0	0	0	0	0	0	1	1	0	0	1	1	0	2
	>1	13	0	0	0	0	0	0	0	0	0	0	1	7	6	7	7
Totals		115	42	32	21	16	5	25	30	36	32	57	38	45	70	16	94

was less evidence in this direction when Q_6 was 1 to 2 mm., but when associated with right ventricular systolic loading it was sufficient to indicate that a very high pulmonary vascular resistance had not yet been reached. A Q_6 of less than 1 mm. was of no significance in this regard. Both the clinical, physiologic, and operative findings all indicate that cases with a good Q wave in V_6 have a significant degree of diastolic overloading of the left ventricle.

Hemodynamics and the Electrocardiogram

The electrocardiogram is simply one of the various clinical and hemodynamic technics for recognizing systolic and diastolic loading of the heart chambers and in interpreting the various degrees of physiologic and pathologic change in the pulmonary arteries. Other methods include an estimation of the pulmonary vascular resistance, pulmonary blood flow and pressure, a study of the arterial oxygen saturation, ear oximetry, or biopsy of lung tissue. The effect of acetylcholine on the pulmonary artery pressure should also be included as well as the clinical examination including a chest x-ray, murmur, thrills, pulsating hilar shadows, pulmonary second sound, systolic click, activity of right and left ventricle, and response to exercise. Finally, the age of the child is important.

It is obvious that all these methods provide useful information in their own way, but each has its limitations. The pulmonary vascular resistance is based on a formula involving blood flow and pressure. A variety of factors may influence these two measurements, such as the type of sedation, anxiety, crying, or activity on the part of the patient. The blood pressure may be higher earlier in cardiac catheterization and lower in the later stages. Oxygen contents of heart chambers may vary to some degree with the site of the catheter, the time during the procedure that blood was withdrawn, the systemic and pulmonary blood pressures. Thus the figures presented as pulmonary vascular resistance may be far from accurate.

Ear oximetry gives us an opportunity to study the oxygen content of arterial blood in these patients at rest, with activity, and with the administration of oxygen. Reversal of blood flow through the defect at rest or with exercise may be readily demonstrated by this method, and provides useful information on the state of the pulmonary arteries. There was no evidence of reversal of flow through the defect with exercise, in the group with

normal or left ventricular systolic loading in their electrocardiograms. A number demonstrated reversal in the combined ventricular loading group, the pulmonary vascular resistance appears not to be excessively great. The age in half this group was under 1 year. On the other hand, in the group with isolated right ventricular hypertrophy, oximetry almost invariably showed a reversal of flow with exercise, with a low flow to the lungs, and confirms the impression of high pulmonary vascular resistance. As one might expect, the age in this latter group was considerably older than the combined group, the average being 8 years, and most of them were 6 years.

Biopsy of the lung has been used occasionally to assess the pulmonary vasculature. This is a significant procedure, but the surgeon is limited to a small area (usually the lingula) in taking out a piece of lung, and while a study of such sections may permit one to place the case into one of the six categories described by Heath and Edwards,[16] it has been shown on several occasions that certain patients having some of the most advanced intimal changes in the pulmonary arteries may occasionally respond successfully to closure of the septal defect with a satisfactory drop in pressure in the pulmonary artery.

The clinical examination is most helpful, since the murmur may be fainter and shorter with pulmonary hypertension and marked increase in pulmonary vascular resistance. The thrill may be absent. The hilar shadows show less pulsation, and the heart is smaller. These observations, while most useful, may be far from decisive in solving the problem at hand, but serve as corroborative evidence.

The resistance of the pulmonary vascular bed may be evaluated by injecting acetylcholine into the pulmonary artery.[1, 17] Adams[1] found that approximately one third of a group of children with ventricular septal defects and pulmonary hypertension failed to respond to this drug, with a drop in pressure in the pulmonary artery. All those who were under 7 years of age responded, however.

Age is an important consideration in estimating the possible hemodynamic response to closure of a ventricular septal defect. The few cases with Eisenmenger's complex in childhood were usually in older children. We have seen several such cases over the age of 12 years. The only children that could legitimately be said to fall into this category in our series are those with reversal of flow coupled with high pulmonary vascular resistance. In table 12 one will see that there were 7 cases that might fit this description. Of these 7 cases all but 2 were over 6 years of age. Thus, in the under 7 age-group, our evidence suggests that only 2 per cent may be labeled as having the Eisenmenger's syndrome.

While the pulmonary vascular resistance is high at birth, and this may persist for some time, eventually all in this age group, with rare exceptions, show evidence of some degree of left ventricular loading, indicating a benign pulmonary vascular resistance that would permit corrective surgery. As indicated above we have only 2 cases under 7 years of age that have evidence clinically or hemodynamically that would suggest they would not respond favorably to surgery. DuShane and co-workers[12] reported 10 cases operated on in spite of the fact that their electrocardiographic patterns did not have any of their operable criteria present. Two had a drop in pressure in pulmonary artery and right ventiele postoperatively. The age of this group was not stated, but one would expect it to be chiefly over 6 years of age.

Several observers have reported repeated cardiac catheterization measurements in ventricular septal defect. Very few children with this anomaly have shown any tendency for the pulmonary vascular resistance to change appreciably in childhood. The electrocardiogram may bear on this problem. From this source alone the evidence suggests that, while some cases have a much higher pulmonary vascular resistance in infancy and early childhood than others, it is not of sufficient magnitude to preclude successful surgical closure of the defect before the age of 7 years except in an occasional rare instance. For these vari-

ous reasons we have included age as one of the criteria of operability.

An examination of electrocardiographic patterns in cases followed for several years showed three types of response: 1. The great majority showed a remarkably constant electrocardiogram over the years each case was followed. 2. A modest number (6) showed a disappearance of the normally right dominant pattern in infancy, or a combined loading, and the appearance of a left loading configuration. Another 5 that were normal to begin with, developed evidence of left loading. This has always been a favorable sign, and such children have done well over the years and are good risks at surgery. Close to the first-mentioned cases are those patterns that have right loading when first seen but subsequently developed combined. This is also associated with the infant growing into the child, and the pulmonary vascular resistance apparently falling to a sufficient degree to produce signs of left diastolic loading. 3. Only 1 case developed a purely right loading pattern, while some of those with combined ventricular hypertrophy showed a progressively dominant R wave in V_1 or a deeper S in V_6, or both, but still retained some evidence of left ventricular loading. There are, therefore, signs of variation in the pulmonary vascular resistance with a gradual reduction in the first year sometimes proceeding into the second year. Only a rare exception is not operable between the ages of 2 and 5 regardless of what their electrocardiograms show.

The criteria of DuShane and his associates[12] for selection of cases for surgery with ventricular septal defect are most helpful, in that they isolate a group that is most likely to survive operation providing the technic is adequate. Their criteria were not designed to provide detailed recognition of normal patterns, left loading, right loading, and combined, nor will they tell us which cases will survive surgery and be helped by it when their criteria are not satisfied.

We have found the criteria of DuShane and his associates useful as a baseline to check our own. By their standards our pure right ventricular loading group would be excluded from surgery as would our normal group. Our left loading group would be included. Approximately 70 per cent of our combined ventricular loading group would be included, but 30 per cent would be excluded from surgery. It is these minority groups that deserve special study.

In our pure right ventricular loading group of 14 cases, 2 have already been operated on successfully.

Broader criteria than those suggested by DuShane and co-workers[12] are needed to permit a wider degree of grading of the pulmonary vascular flow and resistance, and thus enhance our ability to assess operability. The problem of the future lies not so much in identifying the groups that are sure to survive and be cured by surgery, as in identifying those that are operable but whose criteria are not so emphatic. The electrocardiogram is a great help in this, but must be used in conjunction with the cardiac catheter findings, oximetry, and age, as well as with the clinical signs.

In assessing a case of ventricular septal defect by the electrocardiogram two steps appear useful: first, an evaluation of the tracing to decide which of the four main groups it falls into, (a) normal, (b) left loading, (c) combined loading, and (d) pure right ventricular loading (table 12). If it is in group (a) or (b) the pulmonary vascular resistance is low and the child is suitable for surgery, provided the technic becomes adequately safe. When it falls into group (c) or (d), that is combined or pure right ventricular loading, the second form of evaluation is then most helpful. This consists of an itemized study of the factors that relate to pulmonary vascular resistance; the ones we consider the most important are listed in table 12; i.e., a tall R in V_6, or a deep S in V_1, a deep Q in V_6 broadening and notching of the P wave in standard lead I coupled with late inversion of the P in V_1, an axis of less than 90°, counterclockwise vector, a pulmonary systemic flow ratio of more than 2, absence or reversal

of flow through the defect, an age under 7 years.

The application of these criteria to the group of combined loading has been discussed previously. Most cases that have one or more of these criteria in the combined group have shown only moderately raised pulmonary vascular resistance. The cases with the least favorable criteria were those that had neither a tall R_6 nor deep S in V_1, nor a deep Q in V_6, but had a pulmonary/systemic flow ratio of less than 2 and an absence of notching and broadening of the P wave. There were only three under 1 year of age that fell into this category, and none of them had reversal of flow. The Q wave in V_6 varied from 1 to 3 mm. and was the only electrocardiographic evidence in favor of surgical correction.

Among those over 1 year of age in the combined loading group that had no tall R_6 or deep S in V_1, or deep Q in V_6, and a flow ratio of less than 2, there were only 3 cases. One of these had notching and broadening of the P wave, one was operated on successfully, and the other had clinical signs indicative of an adequate pulmonary blood flow. None of the 3 cases had reversal of flow through the defect. Again a q wave in V_6 of 1 to 3 mm. was helpful in recognizing the potentialities of a favorable result.

In summary, one can conclude that in the combined loading group there was good evidence that the overwhelming majority are operable and would respond favorably to closure of the ventricular septal defect.

The group that is least likely to respond is that with pure right ventricular loading. None of these satisfied the criteria of DuShane and co-workers,[12] but 2 of the 14 have already been operated on successfully. Such cases may be picked out of this group by the finding of a pulmonary/systemic blood flow ratio of more than 2, or a counterclockwise vector, or an age that is under 7 years, or an absence of reversal of flow through the defect. If one or more of such items are present, the patient may well survive corrective surgery in spite of the unfavorable electrocardiogram. If none of these items is found, the chances of cure or survival are slim indeed.

A rare case of ventricular septal defect with complete right bundle-branch block will show a pattern indicative of right ventricular hypertrophy or loading when such is either not present or the loading is of a minor degree. The electrocardiogram may then be misleading. This was true of a case in our pure right group. This case was classified by cardiac catheterization, which revealed relatively low pressures and low flows in the pulmonary circuit.

Another case with an electrocardiogram indicating right ventricular hypertrophy and complete right bundle-branch block was found, on cardiac catheterization, to have dynamic evidence of high pulmonary vascular resistance. Such cases are less likely to be missed, since the unfavorable electrocardiogram will lead to further investigation.

We have concluded, therefore, that when complete right bundle-branch block is present it is important to investigate the child fully with adequate blood flow studies.

Summary

One hundred and nineteen cases of ventricular septal defect in infancy and childhood have been reviewed, with special reference to the electrocardiogram. The changes in the electrocardiogram were related to the hemodynamics found at cardiac catheterization, and particularly the pulmonary to systemic blood flow ratios, pulmonary artery pressures, and oximetry. They were also studied in relation to the groups of cases that obviously had a low pulmonary vascular resistance with or without diastolic loading of the left ventricle. Survival of a patient following closure of the defect with a drop in pulmonary artery pressure was also taken as a sign that the pulmonary vascular resistance was not excessive. The patients with clinical and hemodynamic evidence of a high pulmonary vascular resistance were also evaluated in relation to the electrocardiogram.

The information obtained from the electrocardiogram may be graded according to degree of severity: (a) normal electrocardiogram, (b) left ventricular loading, (c) combined loading, (d) isolated right ventricular

loading. These groups may be further graded depending on the diminishing number of signs listed below.[1–7] A detailed review of these four groups in relation to the following criteria may allow one to identify a low or only moderately raised pulmonary vascular resistance, or one that is sufficiently moderate to permit successful corrective surgery in the pediatric age group:

1. An R in V_6 over 20 mm.
2. A Q in V_6 of 4 mm. or over.
3. An S in V_1 over 25 mm.
4. A Q in V_6 of 2 mm. or more when associated with evidence of right ventricular loading.
5. An axis of less than 90°.
6. Counterclockwise vector.
7. Broad notched P waves in standard leads I or II, with late inversion in V_1.

As a rule, several of these criteria occur together, but even if only one of them is present, one may conclude that the pulmonary vascular resistance is not excessive. Further support to this conclusion is evident if any of the above 7 items are accompanied by one or more of the following: (x) a pulmonary blood flow that is twice systemic, (y) an absence of reversal of flow through the defect either at rest or with exercise, (z) an age under 7 years.

Among the 119 infants and children with ventricular septal defect, over 90 per cent appeared to have a sufficiently low pulmonary vascular resistance to be operable provided the surgical technic is adequate and provided complete heart block does not occur.

Age appears to be an important factor in assessing the likelihood of success at surgery. Only an exceptional case shows hemodynamic findings indicating inoperability before the age of 7 years.

During the first year of life many cases of ventricular septal defect have signs of left ventricular loading appear or increase, suggesting a favorable trend in the pulmonary vascular resistance. Until surgical technic makes operation more readily feasible in infancy, the optimum age of correction would appear to be between 2 and 7 years.

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Please do not conclude that I argue for medical protection and care as the *summum bonum of* existence. Man cannot live by bread alone, even when it is whole wheat and reinforced with minerals and all the known vitamins. There are greater ends in living than health. These ends can be attained by those who are not even in perfect health. The same is true of food, housing, and clothing—not particularly rewarding as ends in themselves, but, like health, of considerable importance as means to whatever ends you may deem worthy of living for. In claiming that health is as important as food, shelter, and clothing, I do not imply that it is more important, nor even that health is as important as truth, beauty, or love. But I like to imagine that at the end of a year's prosaic labors in a hookworm campaign in, say, South America, a public health officer encountered a seller of musical instruments who said, "Senhor Doutor, I thank you for your work, because now the people are well enough to sing.' Though different races find each other's because I have sold this year more violins and guitars in this village than ever before, arts, philosophies, and religions not always acceptable, there is a notable amount of agreement everywhere that health wherewith to follow and practice them is good.—Alan Gregg, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 79.

Effect of Breathing Oxygen on Pulmonary Artery Pressure and Pulmonary Vascular Resistance in Patients with Ventricular Septal Defect

By HIRAM W. MARSHALL, M.D., H. J. C. SWAN, M.D., HOWARD B. BURCHELL, M.D., AND EARL H. WOOD, M.D.

IN 1946 von Euler and Liljestrand[1] demonstrated that the pulmonary artery pressure in the cat was increased when the animal breathed a gas mixture of low oxygen content. Comparable results have been demonstrated in other species, including man.[2-4] In spite of a degree of variability in the results of experiments designed to elucidate the mechanism of this response, most studies suggest that hypoxia can cause the pulmonary vessels to constrict. Further studies[5, 6] on the comparative effects of breathing a gas mixture of low oxygen tension in one lung while breathing a gas mixture of normal oxygen tension in the other suggest that constriction takes place in the vessels of the hypoxic lung.

Relatively little attention has been paid to the effect exercised on the pulmonary vascular bed by high oxygen tension in the inspired air, although a fall in pulmonary artery pressure has been demonstrated in man, both with normal pulmonary circulation and with pulmonary hypertension.[7-10] Further, the timing and sequence of events in relation to the change in the oxygen concentration in the inspired gas mixture have not been clearly described.

The present study concerns the effect of breathing gas mixtures of high oxygen tension on the pulmonary and systemic arterial pressures and vascular resistances in 31 patients with ventricular septal defect and varying degrees of elevation of pulmonary artery pressure. Particular attention has been given to the timing of the effects on the pulmonary vascular bed and the changes in the systemic arterial oxygen saturation and heart rate also produced by the change from breathing air to breathing oxygen, and to the interrelation of these events.

The data indicate that in patients with a ventricular septal defect a significant decrease in pulmonary vascular resistance is associated with breathing of high-oxygen mixtures. The decrease in pulmonary artery pressure and heart rate followed by a few seconds the increase in oxygen saturation of systemic arterial blood.

Material and Methods

The diagnosis of ventricular septal defect was considered clearly established on the basis of findings from clinical examination and cardiac catheterization. In 11 of the 31 cases, the diagnosis was verified at operation for correction of the defect. The average age of these 31 patients was 16 years, with a range of 7 months to 43 years.

Measurements

The cardiac catheterization was performed with the technics and instrumentation described previously.[11, 12] The procedure was carried out under rectal tribromoethanol (Avertin) anesthesia[13] in 13 of the younger patients, the remaining 18 having been studied while awake, but after administration of ½ grain codeine and 1½ grains secobarbital (Seconal). Arterial oxygen saturation was recorded by ear oximeters.[14] Intracardiac pressures were recorded and the presence of arterialization in the right ventricle was established. A pulmonary artery wedge pressure was obtained, and then the catheter was positioned in the pulmonary artery. A needle was inserted into the radial or femoral artery. Expired air was collected for 5 to 10 minutes in a large-volume, low-resistance plastic balloon. The volume of the gas was measured and its composition analyzed immediately by the Haldane method for the calculation of oxygen consumption. Midway during the determination of oxygen uptake, blood samples were drawn simultaneously from a systemic

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artery and the pulmonary artery for measurement of oxygen content and capacity. Pulmonary and systemic arterial pressures and other variables were recorded midway during the withdrawal of these blood samples.

Continuous simultaneous recordings of the pulmonary and systemic arterial pressures, arterial oxygen saturation, and other variables were obtained as the gas mixture being breathed by the patient was changed suddenly from room air to a high (95 to 99.5 per cent) oxygen mixture. In 14 of the 31 cases the oxygen was delivered via a low-resistance, small dead-space system, incorporating a carbon dioxide absorber and containing approximately 35 liters of a mixture of 95 per cent oxygen and 5 per cent nitrogen after equilibration with the subject's respiratory gases. The oxygen consumption while breathing oxygen, measured over a 3-minute period after an interval averaging 7½ minutes of oxygen breathing, was found to be increased over the values obtained while breathing air by an average of 11 ml. per sq. meter of body surface ($p = 0.05$). The remaining 17 patients breathed oxygen via a modified BLB face mask which had a small dead space, and the flow of oxygen was set at a rate high enough to prevent appreciable rebreathing of the expired air. In these 17 cases the oxygen consumption while breathing air and while breathing oxygen was assumed not to differ significantly for the purpose of calculation. During the determination of oxygen consumption from the closed-circuit spirometer or during the period of oxygen breathing from the mask, blood samples again were withdrawn from the pulmonary and systemic arteries for determination of the oxygen capacity and content, and pressures were recorded from these sites.

Calculations

Systemic (Q_s) and pulmonary (Q_p) blood flows while breathing air and oxygen were calculated by means of the standard Fick equations. The oxygen content of the mixed venous blood was determined by averaging the contents of superior and inferior caval blood in all cases while breathing air and in 30 of the 31 cases while breathing oxygen. If the oxygen saturation of the arterial blood was less than 95 per cent while the subject breathed air, and the right-to-left shunt calculated by the oxygen saturation data was similar to the right-to-left shunt determined by the indicator-dilution technics,[15] the total oxygen content of the pulmonary vein blood was taken to be 98 per cent of the oxygen capacity plus 0.3 ml. per 100 ml. of blood.

In two of the children catheterized under anesthesia, the degree of desaturation of arterial blood was greater than could be accounted for on the basis of right-to-left shunts determined from dilution curves and was considered to be due in part to desaturation of pulmonary vein blood associated with deficient pulmonary ventilation. In these two cases the oxygen saturation of the pulmonary vein blood was calculated from the magnitude of the right-to-left shunt determined by the dye-dilution technic[15] and the oxygen-saturation values of the mixed venous and arterial bloods. Always when the patients breathed oxygen, the pulmonary vein blood was assumed to contain 1.8 ml. of oxygen per 100 ml. of blood in dissolved form.[16]

Systemic and pulmonary resistances (pressure/flow ratios) were calculated by the usual equation.

Findings

Original photographic recordings showing the immediate response of pulmonary and systemic arterial pressures and the change in arterial oxygen saturation and heart rate during the change from breathing air to breathing oxygen are given in figure 1. In this patient (who was 8 months old), the arterial oxygen saturation began to increase within 3 seconds after the change to breathing oxygen, and the pulmonary artery pressure commenced its decline within 10 seconds after the change to oxygen. Systemic arterial pressure was not demonstrably changed; the heart rate decreased slightly.

The average values and the variability of the immediate effects of the change from breathing air to breathing oxygen in 28 of the patients are shown in figure 2. The increase in systemic arterial oxygen saturation began 5 (2 to 9) seconds after the start of breathing oxygen. As shown in figure 3, the decrease in pulmonary artery pressure followed the change in systemic arterial oxygen saturation in every instance, the interval averaging 8 (1 to 20) seconds. Of the decrease in pulmonary artery pressure during the first 3 minutes, 60 per cent occurred in the first 30 seconds; and only a slight further decrease in pulmonary artery pressure and in heart rate was recorded in the period from 3 minutes to 10 minutes after the change from breathing air to breathing oxygen.

The averages and ranges of the oxygen consumption and heart rates and of the pulmonary and systemic arterial pressures, blood

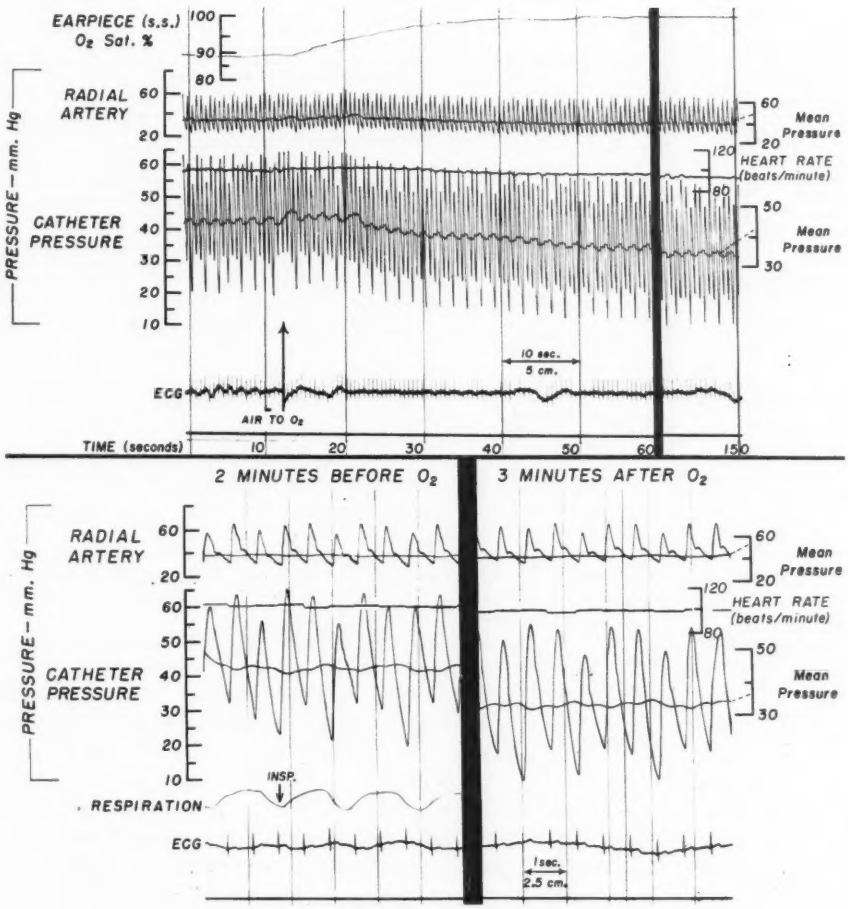

Figure 1

Effects of change from breathing air to breathing 99.5 per cent oxygen on systemic and pulmonary arterial pressures, heart rate, and arterial oxygen saturation in an 8-month-old boy with ventricular septal defect (diagnosis confirmed at operation). Upper panel shows continuous recording (paper speed: 5 mm. per second) from this patient during change (marked by vertical arrow) from air to oxygen. Note that arterial oxygen saturation began to increase within 3 seconds and pulmonary artery pressure to decrease within 10 seconds after change from air to oxygen. Arterial pulse and mean pressures were recorded simultaneously by double galvanometer assemblies.[11] (Reproduced with permission from: Savard, M., Swan, H. J. C., Kirklin, J. W., and Wood, E. H.: Hemodynamic alterations associated with ventricular septal defects. Symposium on congenital heart disease, p. 141.) The lower panel shows recordings taken at a paper speed of 25 mm. per second 2 minutes before and 3 minutes after the change from air to oxygen. Note the decrease in pulmonary artery pressure and heart rate with relatively little change in systemic artery pressure.

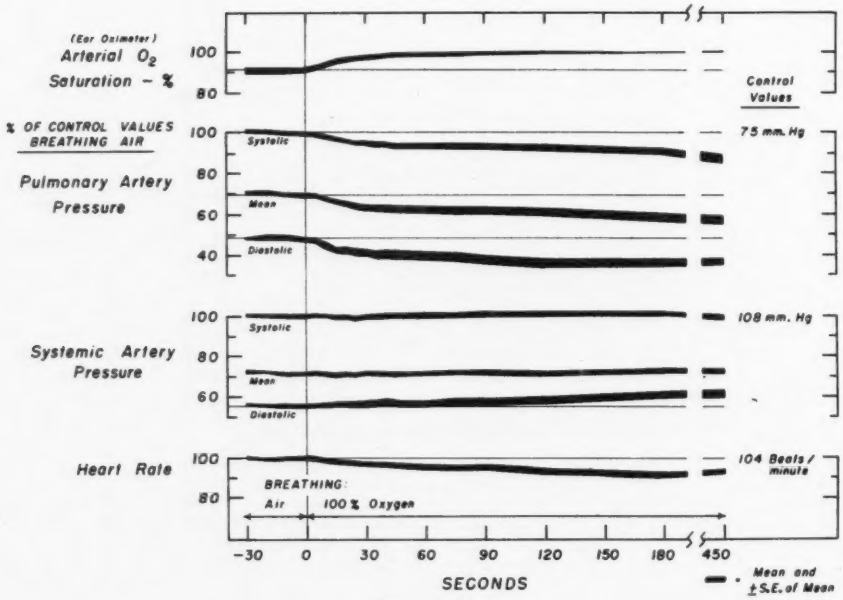

Figure 2

Interrelation of cardiovascular effects produced by change from breathing air to breathing oxygen in 28 patients with ventricular septal defect. Pulmonary and systemic arterial pressures and heart rate are expressed as percentages (scale at left) of control values (indicated at right) which were obtained while breathing air. The wide lines representing the variables measured indicate the mean plus and minus one standard error. Note that the increase in arterial oxygen saturation which occurs within 5 seconds from the change from breathing air to oxygen (marked by vertical line) is followed within 10 seconds by a decrease in pulmonary artery pressure and heart rate.

flows, and resistances obtained from all patients while breathing air and after an average of 7½ (5 to 17) minutes of breathing oxygen are given in table 1. The directional changes were independent of the severity of the pulmonary hypertension and of the use of anesthesia. For the group there was a significant fall in pulmonary artery systolic, mean, and diastolic pressures, although the pulmonary artery pressure increased slightly in two patients. The mean pulmonary artery wedge pressure was not changed significantly. The pulmonary blood flow was increased by an average of 32 per cent (fig. 4). However, four of the six adult patients without pulmonary hypertension showed a small decrease in pulmonary blood flow.

Calculated pulmonary pressure/flow ratios (resistances) decreased by an average of 36 per cent (fig. 5). The decrease was least among adult patients without pulmonary hypertension, and in one of the six there was a slight increase. The magnitude of the change in resistance in eight patients without pulmonary hypertension was similar to that in 18 normal subjects studied in this laboratory (fig. 6).[8] Although the pulmonary artery wedge pressure was not measured in all patients, among the 14 from whom values during the breathing of air and of oxygen were available the average decline in pulmonary "arteriolar" resistance was from 750 to 455 dynes sec. cm.$^{-5}$.

The changes in resistance were not directly correlative with the age of the patients. All the patients aged 10 years and younger showed large decreases in pulmonary resistance while breathing oxygen. Several of the patients in the older groups, including some in middle

age, also showed changes of the same order of magnitude as the changes in the children. Among the older patients were several in whom the changes in pulmonary resistance were insignificant. The majority of these patients, however, were those without severe pulmonary hypertension.

Among the whole series, the average systemic blood flow decreased by 15 per cent ($p = 0.02$), though in seven patients the systemic flow increased slightly. The average systemic resistance was increased by 25 per cent. This change was due to a substantial increase in systemic resistance among the younger patients. In patients aged 12 years and more, the average systemic resistance did not change significantly during the breathing of oxygen. The absolute magnitude of the decrease in pulmonary vascular resistance was greater in patients with fairly severe degrees of pulmonary hypertension than for those with mild or no pulmonary hypertension (figs. 7 and 8). The percentage of decrease in pulmonary vascular resistance, however, tended to be greatest where pulmonary hypertension was moderately severe and to be somewhat less in the cases of very severe pulmonary hypertension, where the pulmonary vascular resistance equaled or exceeded systemic vascular resistance.

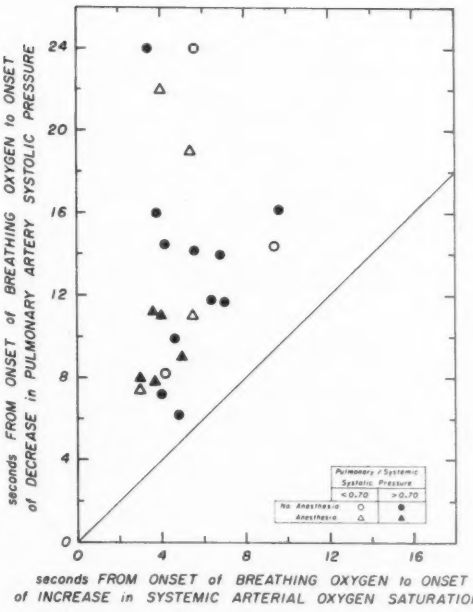

Figure 3

Relation of time from onset of breathing oxygen to onset of increase in oxygen saturation of arterial blood and onset of decrease in pulmonary artery systolic pressure in 23 patients with ventricular septal defect. Patients were excluded whose change in pulmonary artery pressure was too small or gradual to be accurately timed. Patients have been distinguished on the basis of severity of pulmonary hypertension (pulmonary artery systolic pressure greater or less than 70 per cent systemic artery pressure). Diagonal is line of identity. Note that decrease in pulmonary artery systolic pressure uniformly followed increase in oxygen saturation of systemic arterial blood.

Discussion

Considerations on Measurement

Because the pulmonary vascular resistance normally is low, only relatively large changes in this resistance produce changes in pulmonary artery pressure of an absolute magnitude sufficient for measurement with reasonable accuracy in the intact organism. Accurate interpretation of the cause of such changes in pressure is even more difficult in the light of changes that may occur concomitantly in blood flow, heart rate, respiration, and other variables. The lack of agreement among the results from the numerous studies of factors affecting the pulmonary circulation probably is due in great measure to the large errors of observation and interpretation inherent in most of these investigations.

In the presence of pulmonary hypertension, however, the percentage of error in such observations is reduced; for if blood flow is unchanged, the absolute magnitude of the change in pressure caused by a given percentage change in pulmonary vascular resistance is directly related to the level of the pulmonary artery pressure. A large share of patients with ventricular septal defect have pulmonary hypertension and thus constitute a suitable group for a study of the response of the pulmonary circulation to changes in the oxygen tension of the inspired gas mixture. Since in normal subjects also the breathing of oxygen causes a small decrease in pulmonary artery

Table 1

Averages (and Ranges) of Circulatory Variables in Thirty-one Patients with Ventricular Septal Defect While Breathing Air and after Seven and a half (Five to Seventeen) Minutes of Breathing 95 to 99.5 Per Cent Oxygen*

	Breathing air	Breathing oxygen	Difference	*p* Value
Oxygen consumption, ml./min./M.^{2}	211 (153-279)	222† (159-303)	+11 (—18 to +38)	0.05
Heart rate, beats/min.	104 (64-141)	96 (62-143)	—8 (—20 to +10)	0.001
Mean pulmonary artery wedge pressure,‡ mm. Hg	10.1 (5-18)	11.1 (7-20)	+1.0 (—4 to +6)	0.2
Pulmonary artery pressure, mm. Hg				
Systolic	75 (18-124)	66 (15-124)	—9 (—23 to +12)	0.001
Diastolic	37 (7-72)	32 (7-68)	—5 (—22 to +3)	0.001
Mean	53 (11-86)	46 (11-81)	—7 (—22 to +3)	0.001
Systemic artery pressure, mm. Hg				
Systolic	108 (62-166)	107 (60-161)	—1 (—16 to +23)	0.6
Diastolic	61 (30-98)	65 (32-89)	+4 (—12 to +23)	0.3
Mean	78 (41-119)	79 (42-114)	+1 (—13 to +23)	0.5
Pulmonary blood flow, L./min./M.^{2}	6.3 (1.8-19.4)	8.3 (2.0-24.9)	+2.0 (—2.1 to +15.7)	0.001
Systemic blood flow, L./min./M.^{2}	4.1 (1.6-8.2)	3.5 (2.0-7.0)	—0.6 (—4.5 to +1.2)	0.02
Pulmonary vascular resistance,§ dynes sec. cm.$^{-5}$	970 (120-2520)	616 (110-1930)	—354 (—1280 to +10)	0.001
Systemic vascular resistance,§ dynes sec. cm.$^{-5}$	1635 (790-3530)	2040 (930-4550)	+405 (—740 to +1490)	0.01
R_p/R_s‖	0.57 (0.10-1.36)	0.33 (0.09-1.00)	—0.24 (—0.75 to +0.03)	0.001

*Except for measurements of oxygen consumption while breathing oxygen and measurements of wedge pressures, values for all parameters were obtained from each of the 31 patients both when breathing air and when breathing oxygen.

†Oxygen consumption while breathing oxygen was measured in 14 patients.

‡Mean pulmonary wedge pressures were obtained from 14 patients while breathing air and while breathing oxygen.

§In these values for vascular resistance, no correction was made for pulmonary or systemic venous pressure.

‖Ratio of pulmonary to systemic vascular resistance.

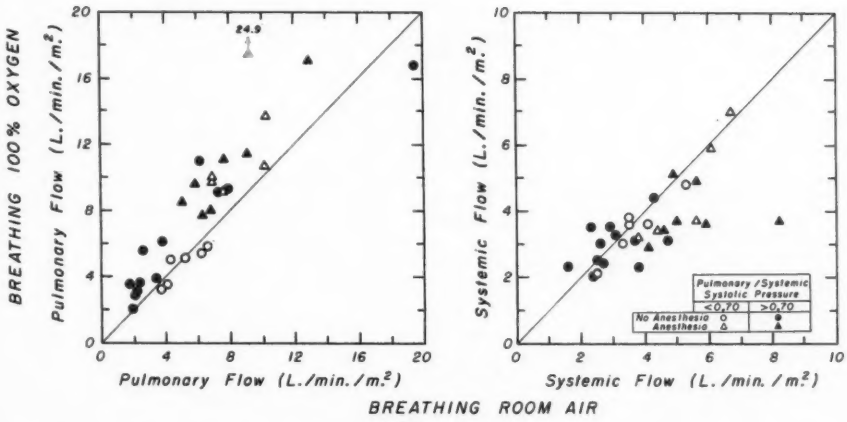

Figure 4

Relation of pulmonary and systemic blood flow in patients breathing air to values obtained after breathing 95 per cent to 99.5 per cent oxygen for 7½ (5 to 17) minutes in 31 patients with ventricular septal defect. Diagonal is line of identity. Pulmonary flow (left panel) was increased or unchanged in all but five patients while breathing oxygen. Changes in pulmonary flow among the group of six adult patients who had normal pulmonary artery pressures (open circles) were not significant. Changes in systemic blood flow (right panel) during the period of oxygen breathing were variable; however, the decrease in systemic artery blood flow was statistically significant (average decrease = 0.6 L./min.; p = 0.02). Note that this comparison shows no difference between patients studied with or without anesthesia.

pressure and a significant decrease in heart rate, it is likely that the normal pulmonary circulation responds in a similar manner—although this is by no means certain.

Decrease of Pulmonary Resistance

The patients studied had a wide range of pulmonary vascular resistances that included those encountered in normal subjects. As would be expected, the smallest absolute changes with breathing of oxygen were observed in the patients with low pulmonary resistance values and without pulmonary hypertension when they breathed air. Even in those patients with severely elevated pulmonary vascular resistances, a decrease of considerable magnitude was evident.

Although the absolute decrease in pulmonary vascular resistance generally remains large among these patients with pulmonary hypertension, the proportionate decrease in resistance appeared to be less in those patients in whom the pulmonary hypertension was most severe and in whom the pulmonary/systemic resistance ratio approached or exceeded 1.0. This degree of elevation of pulmonary resistance is indicative of the presence of severe organic changes in the pulmonary vessels, and it would be expected that the capacity of such vessels to dilate would be limited.[17] Certain other patients with idiopathic pulmonary hypertension, in whom the pulmonary resistance values were much higher than any obtained in this study, showed no significant decrease in pulmonary vascular resistance while breathing oxygen.[18]

Since no change in pulmonary artery wedge pressure was observed in those patients in whom it was measured, the decline in resistance to pulmonary blood flow is almost certainly due to a fall in the component of this resistance which exists between the large pulmonary arteries and the left atrium—that is, the pulmonary arteriolar or vascular resistance. This decline suggests that the hindrance offered by the smaller pulmonary vessels to flow through them is reduced during breathing of oxygen. Recent publications have stressed the need for extreme care in the in-

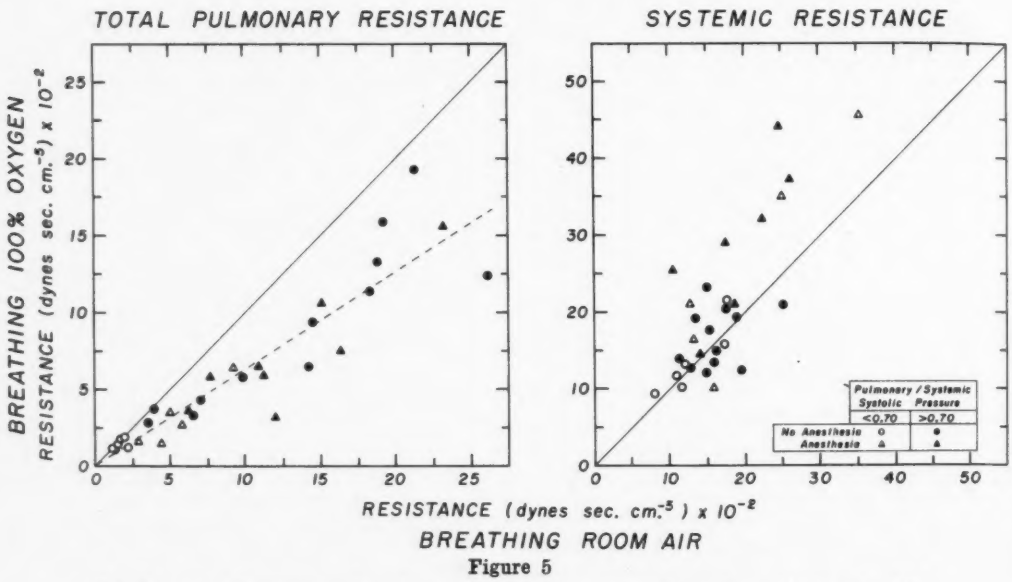

Figure 5

Relation of pulmonary and systemic pressure/flow ratios (vascular resistances) while breathing air to those while breathing oxygen for 7½ (5 to 17) minutes in 31 patients with ventricular septal defect. Patients have been distinguished as in figure 3. Dashed line in left panel shows average decrease in pulmonary vascular resistance (36 per cent) which occurred when patients were breathing oxygen. Note uniform decrease in pulmonary vascular resistance while breathing oxygen. Although the response of systemic vascular resistance (right panel) was more variable, its average increase was 405 dynes sec. cm.⁻⁵ (p = 0.01).

terpretation of such findings.[19] In the conditions under study, however, there is no reason to suspect that intrathoracic pressure changed significantly and, so far as could be determined, there was no significant change in the breathing pattern. The heart rate slowed slightly and the stroke volume increased. Apart from the increase in the stroke volume, none of these factors would be expected to change the calculated vascular resistance. Since the intrathoracic pressure apparently remained virtually unchanged while the intrapulmonary arterial pressure fell, the transmural pressure—that is, the effective distending pressure in these vessels—was significantly reduced. The association of a decrease in transmural pressure with a reduction in vascular resistance strongly suggests a decrease in tone of the pulmonary blood vessels. These results demonstrate that the pulmonary vascular bed remains labile and that vasomotor tone plays a significant part in the pulmonary hypertension which is present in many of these patients.

Timing of Changes

The temporal relation of the change in pulmonary artery pressure to certain other parameters is clearly demonstrated. The initial change in this pressure usually was evident within 15 seconds of the first inspiration of oxygen as compared to the striking increase in alveolar oxygen tension that would occur immediately upon the first inspiration. At a respiratory rate of 20 per minute the alveolar pO_2 would have increased to approximately three to four times the control values during this 15-second interval. The beginning of the decrease in pulmonary artery pressure seems more clearly related to the increase in systemic arterial oxygen saturation than to the increase in alveolar pO_2, because the time at which the decrease in pulmonary artery pres-

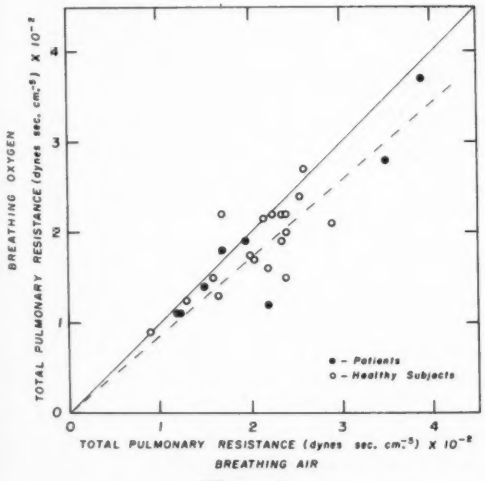
BREATHING OXYGEN
TOTAL PULMONARY RESISTANCE (dynes sec. cm.⁻⁵) X 10⁻²
TOTAL PULMONARY RESISTANCE (dynes sec. cm.⁻⁵) X 10⁻²
BREATHING AIR
● – Patients
○ – Healthy Subjects

Figure 6

Comparison of changes in pulmonary pressure/flow ratios produced by breathing oxygen in 18 healthy subjects studied by Barratt-Boyes and Wood[8] and in the eight patients with ventricular septal defect in this study in whom pulmonary vascular resistance was less than 400 dynes sec. cm.⁻⁵. Dashed line shows average decrease in pulmonary vascular resistance (18 per cent) of the healthy subjects while breathing oxygen. The responses shown by the eight patients fall within the distribution of values for the healthy subjects.

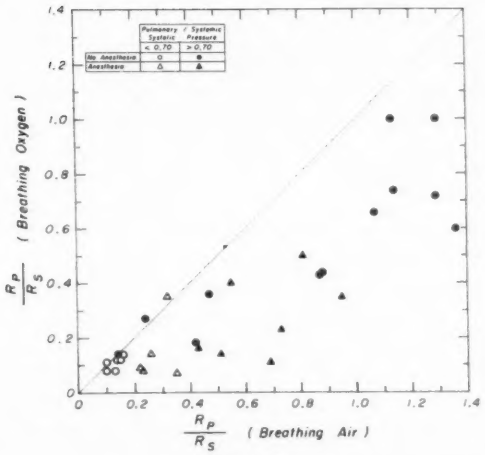

Figure 7

Comparison of the ratios of pulmonary vascular resistance to systemic vascular resistance obtained during breathing of oxygen with the ratios obtained during breathing of air in 30 patients with ventricular septal defect. Diagonal indicates an unchanged ratio. Note consistency of decline in this resistance ratio with breathing of oxygen, which is seen even in the presence of a severe increase in pulmonary resistance.

sure became evident always came after the increase in systemic arterial saturation began, and usually during the phase in which the increase in saturation was most rapid (figs. 1, 2, and 3). Since the declines in heart rate and pulmonary artery pressure occur almost simultaneously, the bradycardia and the decline in pressure may be mediated by the same mechanism.

Mechanism of Response

There is no direct information on the mechanism whereby the inspiration of a high-oxygen mixture causes a reduction of pulmonary vascular resistance. However, the effect of the inspiration of gas mixtures of lowered oxygen tension has been extensively studied. Since the change in pulmonary artery pressure and pulmonary vascular resistance appears to be diametrically opposite when gas mixtures of high or low oxygen content are breathed, it is likely that they represent extremes of the same response, and that when ambient air is breathed, the pulmonary blood vessels are maintained in an intermediate state of tone.

The results of the different studies designed to elucidate the mechanism of response to hypoxia are various. In a recent paper, Liljestrand[20] concluded that hypoxia acts on pulmonary vessels by liberation of lactic acid and thereby may effect local regulation of the relation between pulmonary blood flow and ventilation. The previous experimental work was summarized and reviewed in the light of his own most recent findings.

The present studies contribute to an understanding of the mechanism of response in two ways: (1) they define the period that elapses before the response becomes operative and demonstrate it to be of the order of seconds; (2) they indicate that pulmonary artery wedge pressure does not fall during the breathing of oxygen. If the pulmonary artery wedge pressure measures pulmonary capillary pressure, then all of the change in vascular

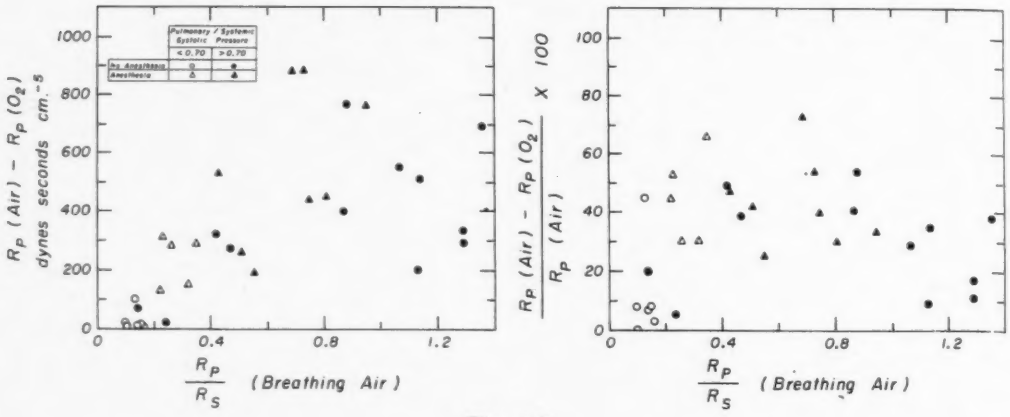

Figure 8

Comparison of decrease in pulmonary resistance during breathing of oxygen with the level of the ratios of pulmonary vascular resistance to systemic vascular resistance obtained during breathing of air in 31 patients with ventricular septal defect. Note that both the absolute changes (left panel) and relative changes (right panel) tend to be greatest in those patients with moderately severe increases in pulmonary vascular resistance (R_p/R_s = 0.40 to 0.90).

tone occurred in the precapillary vessels. If, as more probably is true, the pulmonary artery wedge pressure represents the pressure operative in the next pulmonary vascular bed downstream to the wedged catheter in which flow is occurring, then some change of tone in the capillaries and small vessels might not produce detectable changes in the wedge pressure. However, in the presence of pulmonary hypertension with increased vascular resistance, which is almost certain to be precapillary, the relatively large magnitude of the change in vascular resistance in a number of patients indicates that this response must have involved the precapillary vessels.

Because of the presence of a left-to-right shunt via the defect in these patients, the pulmonary artery oxygen saturation, unlike that in persons without septal defects, would rise coincidentally with the change in systemic arterial oxygen saturation. It is of considerable interest, therefore, that the temporal relation of the increase in arterial oxygen saturation to the subsequent decrease in pulmonary artery pressure is closely similar in this group of patients with left-to-right shunt to the time sequence observed in patients with pulmonary hypertension who respond with a decrease in pressure but do not have a septal defect. This fact is compatible with the interpretation that these effects are not triggered by the increase in oxygen content of pulmonary artery blood. Furthermore, whatever the mechanism, it was not demonstrably affected by the anesthetic agents used to induce general anesthesia in some of the patients included in this study.

Assumptions Used in Calculations

The assumptions concerning the use of the pulmonary artery wedge pressure and the oxygen saturation of pulmonary vein blood have been discussed already, as has the relation of oxygen consumption values when the subject breathes air and breathes oxygen.

Data as to whether samples of blood drawn from the pulmonary artery in the presence of ventricular septal defect are uniformly mixed in regard to oxygen content are not available. It is the practice in this laboratory to obtain multiple samples of blood in rapid succession from the pulmonary artery and its main branches.[11] In 15 of the patients in this series, the average maximal variation in oxygen saturation of multiple (two to six) samples of blood drawn from different locations

in the pulmonary artery and its main branches during the breathing of either air or oxygen was 1.4 per cent. This small variation permits the conclusion that in the presence of a ventricular septal defect the mixing of blood in the pulmonary artery is, for practical purposes, uniform.

The values for pulmonary and systemic arterial pressures, arterial oxygen saturation, and heart rate approached closely, within 3 minutes after the start of breathing oxygen, the values obtained at the time blood samples were drawn for the calculation of pulmonary and systemic blood flows (5 to 17 minutes after the change to oxygen). Hence it seems reasonable to assume that a steady state in regard to metabolic equilibrium was attained. The average variation between the percentage of oxygen saturation of blood samples drawn from the pulmonary artery through a cuvette oximeter for Van Slyke analysis and that of a second sample drawn within an average of 12 minutes later was only 0.7 per cent, which is strong additional evidence for metabolic stability.

Phasic variations in the oxygen content and flow of blood at the sampling sites probably are of greater magnitude in patients with ventricular septal defect than in persons without intracardiac shunts. However, it appears unlikely that the direction and magnitude of errors these effects could cause in determination of flow by the Fick method would be influenced to a significant degree by the change from breathing air to breathing oxygen. The similarity in the response to breathing oxygen by patients with atrial septal defect[10] and with patent ductus arteriosus[9] lends support to this conclusion.

Summary and Conclusions

During cardiac catheterization, pulmonary and systemic arterial pressure, arterial oxygen saturation, respirations, and heart beats were recorded continuously during the change from breathing air to breathing 95 to 99.5 per cent oxygen in a series of 31 patients with ventricular septal defect. In addition, pulmonary and systemic blood flows were measured under the two circumstances.

Systemic arterial oxygen saturation began to increase about 5 seconds after the change from breathing air to breathing oxygen. Within a few seconds thereafter the pulmonary artery pressure and heart rate began to decrease. After approximately 3 minutes the changes in these parameters appeared essentially complete.

The pulmonary blood flow increased by an average of 32 per cent while systemic flow decreased by 15 per cent during breathing of the high-oxygen mixture. No consistent change in pulmonary artery wedge pressure was observed. The average calculated pulmonary pressure/flow ratio (resistance) was decreased by 36 per cent while the average systemic pressure/flow ratio was increased. The occurrence of these changes was independent of the presence of pulmonary hypertension, of the use of general anesthesia, and of the age of the patient.

It is concluded that in patients having ventricular septal defects, the presence of vasomotor tone in the pulmonary vasculature is usual, and that in those having associated pulmonary hypertension, a significant contributing factor is constriction of the precapillary pulmonary resistance vessels.

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On first thoughts it may seem remarkable that scientific work like this should have been performed by a country parson. In the nineteenth century religion and science became mutually antagonistic, and at the present time it is still uncommon to see them in open association; but in the early years of the eighteenth century the Church looked with success to science for support.—A. E. Clark-Kennedy, M.D., M.R.C.P. *Stephen Hales, D.D., F.R.S.* Cambridge, University Press, 1929, p. 76.

The Association of Complete Heart Block and Adams-Stokes Syndrome in Two Cases of Mobitz Type of Block

Case Reports

By JEROME G. KAUFMAN, M.D., FRED W. WACHTEL, M.D., EDWIN ROTHFIELD, M.D., AND ARTHUR BERNSTEIN, M.D.

IN second-degree atrioventricular (A-V) heart block atrial impulses fail to reach the ventricles. The best-known examples are 2:1 A-V block and A-V block with Wenckebach periods. Another more uncommon type of second degree A-V heart block is that of Mobitz.[1] In this situation the P-R interval is fixed, although it may be less than, equal to, or greater than 0.20 second. At intervals a single ventricular beat is dropped, however, resulting in a 3:2, 6:5, 9:8, etc. response.

Examples of this variety of heart block are found mainly in atlases or textbooks dealing exclusively with the arrhythmias.[2-4] Since the emphasis in these publications is on the electrocardiographic mechanism, only short accounts of the associated clinical picture are available. Our interest in reviewing this subject resulted from the observation of two patients with this type of electrocardiogram in whom Adams-Stokes seizures occurred.

Case Reports

Case 1

J. C. R., a 41-year-old white male carpenter was seen by one of us in consultation on January 6, 1959. He had been in good health until August 6, 1958, when on lifting a heavy object he became weak, diaphoretic, and clammy, and was driven home from work. The next morning he developed an episode of syncope, was hospitalized, and suffered about 50 episodes of syncope during the next few days. Electrocardiograms were reported to show complete heart block. Shortly thereafter he became asymptomatic and after a suitable interval was discharged from the hospital.

Physical examination at the time of consultation was entirely within normal limits, except for an irregular pulse. The electrocardiogram showed regular sinus rhythm with a P-R interval of 0.16 second. The P-R interval was constant, but there was no ventricular response to every third P wave. This cycle was constantly repetitive throughout the entire record. The QRS complex was widened to 0.13 second and the configuration was compatible with diaphragmatic infarction and right bundle-branch block (fig. 1A and 1B).

Three months later the physical and electrocardiographic findings were identical with those observed previously (fig. 1C). The patient is reported to be in good health at the time of this report.

Case 2

D. C., a 67-year-old white man, was admitted to the Newark Beth Israel Hospital because of progressive dyspnea and disorientation. He had been treated by one of us for severe pulmonary emphysema and fibrosis and cor pulmonale for many years. He was disoriented, markedly cyanotic, and dyspneic. The blood pressure was 130/60; ventricular rate, 84 and regular; respirations, 44. The lungs were filled with wheezes and rhonchi. An electrocardiogram taken at that time showed regular sinus rhythm with a P-R interval of 0.20 second. The QRS was 0.16 second with marked left axis deviation in the standard leads, a tall R in V_1, equiphasic rs waves in V_2, V_3, and V_4, and rs in V_5 and V_6 (fig. 2A). This record was interpreted as showing evidence of an intraventricular conduction disturbance and myocardial damage.

After several hours the ventricular rate became irregular and another electrocardiogram revealed regular sinus rhythm with an atrial rate of 94. The P-R interval was again 0.20 second. At irregular intervals the ventricles failed to respond to the atrial pacemaker, resulting in periods of 5:4, 4.3, and 3:2 A-V block (fig. 2B). There were no changes in the QRS configuration.

In the subsequent 12 hours several Adams-Stokes seizures were observed. During these periods the electrocardiogram revealed complete heart block (fig. 2C). Somewhat later the patient died during one such seizure.

From the Department of Medicine, Beth Israel Hospital, Newark, New Jersey.

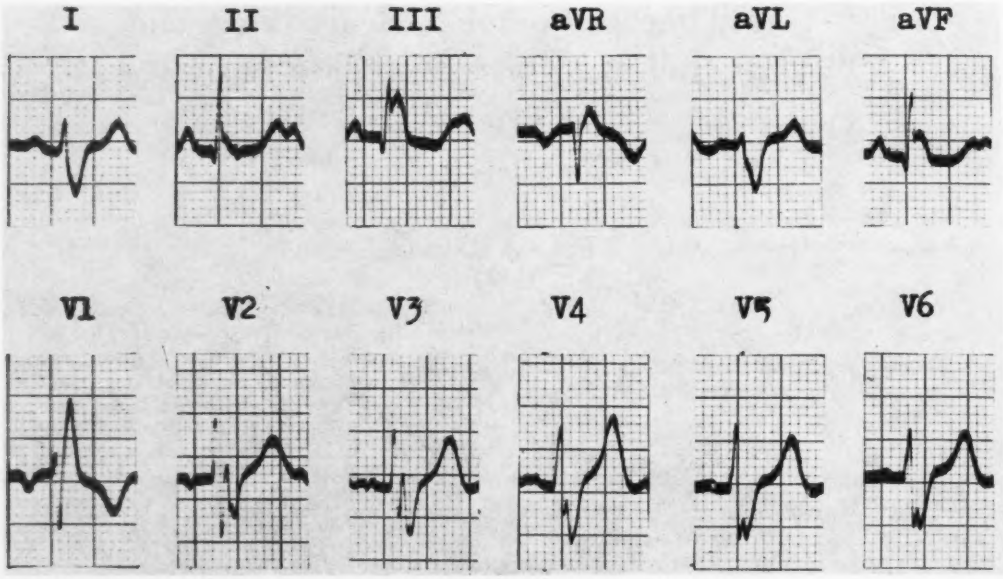

Figure 1A

Electrocardiogram showing a P-R interval of 0.16 second and a QRS duration of 0.13 second. The configuration is that of right bundle-branch block. The Q_2, Q_3, and QaV_F suggest diaphragmatic infarction.

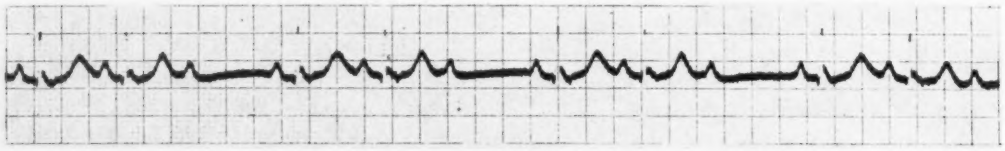

Figure 1B

Continuous tracing of lead II, showing a constant P-R interval of 0.16 second and P-P interval of 0.63 second. There is no ventricular response to every third P wave, resulting in alternating R-R intervals of 0.63 and 1.26 second (3:2 second-degree A-V heart block).

Figure 1C

Continuous tracing of lead II, taken 3 months after figure 1B. There is no essential difference in the arrhythmia or QRS configuration from the original electrocardiogram.

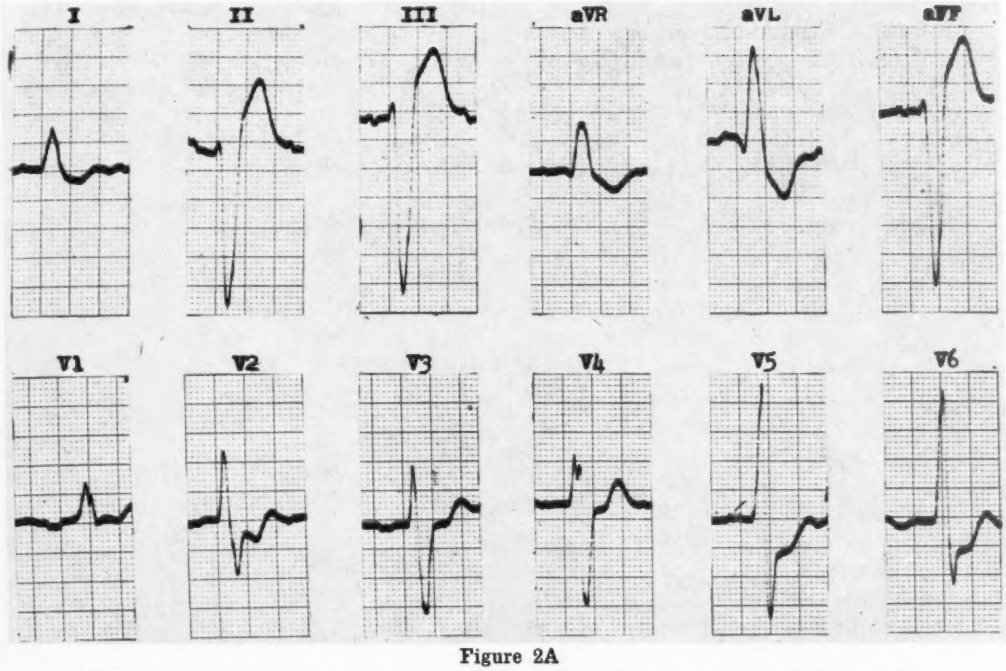

Figure 2A

Electrocardiogram taken soon after admission. The rhythm is regular (not shown). The P-R interval is 0.20 and the QRS duration is 0.16 second. There is marked left axis deviation in the standard leads and a tall R wave in V_1. These findings are interpreted as showing evidence of interventricular conduction disturbance and myocardial damage.

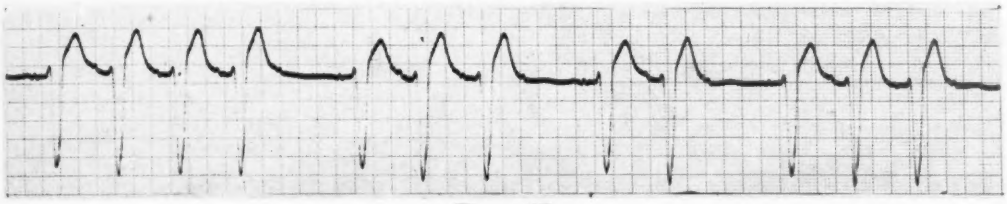

Figure 2B

Continuous tracing of lead II taken 8 hours later, showing a constant P-R interval of 0.20 second and a constant P-P interval of 0.64 second. There is no ventricular response following the fifth, ninth, twelfth, and sixteenth P wave. The sequence is 5:4, 4:3, 3:2 and 4:3 second-degree A-V heart block. The QRS configuration is the same as that in figure 2A.

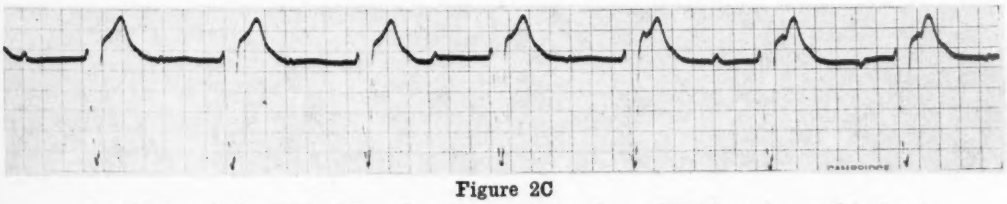

Figure 2C

Continuous tracing of lead II, taken 10 hours after figure 2B. There is complete heart block. The P-P interval varies from 0.68 to 0.74 second, demonstrating sinus arrhythmia. The R-R interval is 1.32 seconds.

Discussion

Patients demonstrating the Mobitz-type block probably have serious organic heart disease. This arrhythmia has not been reported as an example of digitalis toxicity, or other drug toxicity, nor is it seen as a functional disturbance of rhythm in an otherwise normal heart.[5–7]

The arrhythmia in and of itself is one that evidently does not embarrass the cardiac output to a significant extent and is therefore compatible with good cardiac function, as exemplified by case 1. As with other forms of heart block, this arrhythmia may be unstable and may proceed to a more advanced degree of heart block, with the appearance of Adams-Stokes seizures. The latter were present at one time or another in both of our patients, and were also present in the original patient of Mobitz and in Spang's patient.[1, 4] The latter two cases are the only ones available in the literature with clinical histories. The presence of a constantly recurring 3:2 block of this variety, which maintains itself as demonstrated in case 1 is exceptional; we have not been able to discover a similar case.

The Mobitz block has been thought to result from a prolongation of the absolute refractory period of the atrioventricular node; the relative refractory period remains unchanged.[3] This is in contradistinction to the mechanism underlying the Wenckebach phenomenon.

Frequently associated with the Mobitz-type A-V block is a change in the QRS complex. This alteration consists in a widening of the QRS complex to at least 0.12 second or greater, indicative of some type of intraventricular conduction disturbanee. Occasionally these look like right bundle-branch block, while at other times the block is of the indeterminate variety. It is conceivable, therefore, that a dropped ventricular beat could result from intermittent depression of conduction in the functioning bundle branch. In essence, this type of A-V association may at times result from the development of a bilateral bundle-branch block, rather than a block at the level of the A-V node. Both mechanisms could conceivably be operative at various times in the same patient.

Summary

Two cases exhibiting the Mobitz-type of second-degree atrioventricular heart block are reported.

This rhythm may be unstable, and progression to complete heart block and Adams-Stokes seizures has been observed.

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Acute Constrictive Epicarditis Following Infectious Mononucleosis

Case Report

By D. R. Wilson, M.D., S. C. Lenkei, M.D., and J. F. Paterson, M.D.

IT IS KNOWN that infectious mononucleosis may be complicated by myocarditis and pericarditis. This report concerns a young man in whom pericarditis and cardiac tamponade developed into acute constrictive epicarditis in the course of this disease. The clinical diagnosis of constriction was proved by hemodynamic studies and by operation, which was followed by complete recovery.

Cardiac involvement in infectious mononucleosis was reported as early as 1914 by Kirkland and Pruen.[1, 2] They described "cervical adenitis with cardiac complications" in 14 out of 60 patients. However, the evidence for heart involvement was confined to electrocardiographic changes. The Armed Forces Institute of Pathology[3] in Washington has reported that six out of 19 fatal cases of infectious mononucleosis had myocarditis. Pericarditis was first reported in 1946 by Evans and Graybiel.[4] One of their patients was a 20-year-old man in shock due to massive pericardial effusion.

Case Report

Our patient was a 24-year-old man (W.P.), who was admitted to the Toronto Western Hospital on July 24, 1959. Six weeks previously he had a sore throat, followed by slight fever, cough, and pain in the chest. He developed shortness of breath, fullness in the abdomen, vomiting, weakness, and decreasing urinary volume.

On admission he was acutely ill with dyspnea, cyanosis, and jugular venous distention. His blood pressure was 112/105 mm. Hg. No paradoxical pulse was noted. The apical rate was 95 per minute and regular. The heart sounds were of good quality. There was dullness to percussion with diminished breath sounds over the right chest posteriorly. The liver edge was at the level of the umbilicus. His temperature was 101 F.

His chest x-ray on admission (fig. 1) showed blunting of the right costophrenic angle and a globular appearance to the heart. The electrocardiogram on July 27, 1959, showed negative T waves in the limb leads as well as negative T in V_5.

Laboratory data on admission were as follows: Hemoglobin 90 per cent, white cell count 7,000, with 35 per cent lymphocytes and 15 per cent atypical monocytes. Paul Bunnell agglutination was positive in a dilution of 1:1792. The nonprotein nitrogen was 64 mg. per cent. The total proteins were 5.6 Gm., with a normal electrophoretic pattern. The urine was normal on admission and remained so throughout his hospital stay.

Two weeks after admission he developed peripheral edema, bilateral pleural effusions, and a paradoxical pulse of about 15 mm. Hg. The voltage was decreased in the limb leads of the electrocardiogram. On August 10, 1959, he became unconscious twice after severe coughing. The same day 600 ml. of straw colored fluid were removed from his pericardium.

His chest x-ray immediately following pericardiocentesis showed a small amount of air in the pericardial sac (fig. 2).

The pericardial aspiration was followed by transient clinical improvement. Three days after the first pericardiocentesis he developed thrombocytopenic purpura with a platelet count of 70,000. The bone marrow film was compatible with a hemolytic process, although the hemoglobin remained around 90 per cent.

For the first 4 weeks, the patient's daily urinary output was less than 1,000 ml., despite repeated injections of Thiomerin, oral diuretics, and varying amounts of Prednisone. At the end of that time he had a diuresis, during which he lost most of his peripheral edema but retained his pleural and pericardial effusions. The diuresis was followed by a marked drop in his serum sodium and chlorides to 123 and 72 mEq. per liter respectively. He also developed an acute psychosis with hallucinations. After a week of intensive treatment, the low-sodium syndrome was corrected, his psychosis cleared, and the thrombocytopenic purpura disappeared. In August, the patient had eight pleural and four pericardial aspirations. In September and most of October his condition was stationary. Figure 3 is representative of his many chest x-rays during this period. His weight was

From the Cardiovascular Unit, Toronto Western Hospital, Toronto, Ontario, Canada.

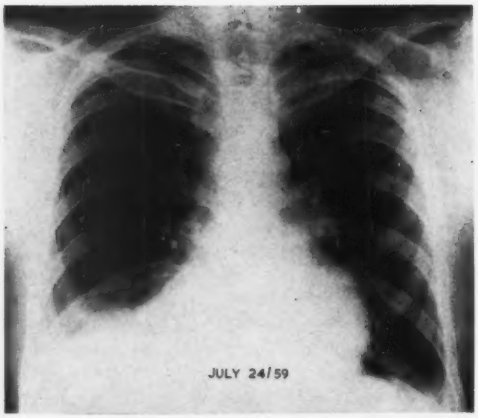

Figure 1

Chest x-ray on admission shows right pleural effusion and a globular appearance to the heart.

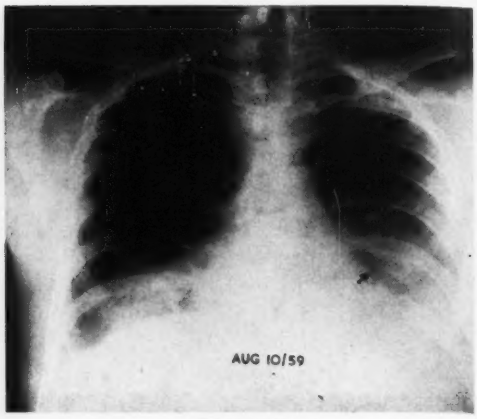

Figure 2

After pericardiocentesis (600 ml.) a small amount of air is seen in the pericardial sac.

Figure 3

X-ray shows bilateral pleural effusions and a pericardial effusion.

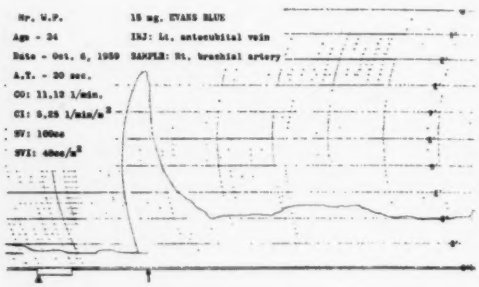

Figure 4

Cardiac-output estimation by the dye-dilution technic. Sampling is by a Waters cuvette attached to a Paul-Cambridge oximeter.

steady around 185 lb. in spite of oral diuretics and repeated injections of Thiomerin. The liver remained at the level of the umbilicus. The jugular venous distention was unchanged, and his pulse pressure rarely exceeded 30 mm. Hg.

Two and a half months after admission, on October 6, a cardiac-output estimation was done by the dye-dilution technic (fig. 4). The appearance time was 20 seconds. The cardiac output was 11.12 liters per minute. The cardiac index was 5.25 liters per minute per M.^{2} Blood volume estimation was within normal limits.

Toward the end of October his condition deteriorated. He started to gain weight, despite continued diuretic treatment, and again developed gross peripheral edema and ascites. His weight reached a maximum of 206 lb. On November 11, 3½ months after admission, he was transferred to the Metabolic Unit where urinary sodium estimations were done. In figure 5 the urinary output and sodium excretion, together with the dietary sodium intake and weight, are shown. With each injection of Thiomerin diuresis with maximal sodium excretion occurred. Between injections the urinary output was low and the sodium excretion practically zero, this despite a sodium intake of less than 400 mg. a day. His weight fell on this rigid sodium restriction from 206 to 183 lb. and then remained stationary. He still had jugular venous distention, pleural effusion, pericardial effusion, and gross ascites requiring abdominal paracentesis several times. The liver remained at the level of the umbilicus.

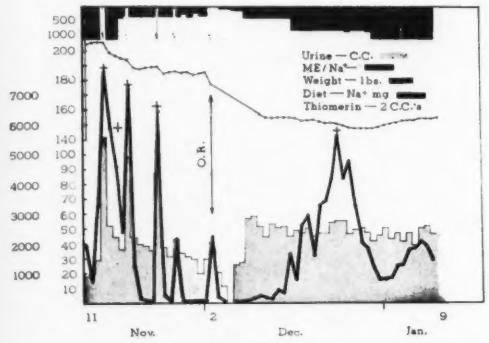

Figure 5

Chart showing urinary volume, urinary sodium excretion, weight, dietary sodium intake, and diuretic treatment. Figures 1,000 to 7,000 on the ordinate represent the patient's daily urinary output in milliliters; 10 to 100, the daily urinary sodium excretion in milliequivalents; 140 to 200, the patient's weight in pounds; and 1,000 to 500, the daily dietary sodium intake in milligrams. It can be seen that sodium and water excretion is maximal after each injection of Thiomerin. Between injections urinary sodium excretion is negligible on continued low dietary sodium intake.

Eight weeks after the first study, a repeat cardiac output estimation was done (fig. 6). The appearance time, which had been 20 seconds, was now prolonged to 27 seconds. The cardiac output fell from 11.12 to 4.19 liters per minute. Fluoroscopic examination showed almost total absence of cardiac pulsations. A diagnosis of acute constrictive epicarditis was made and the patient was referred for surgery (D.R.W.).

Before operation, on December 2, 1959, 4,500 ml. of ascitic fluid and 1,500 ml. of right pleural fluid were removed. When the left chest was opened by an anterior fourth interspace incision, another 1,200 ml. of fluid were obtained. There was almost no cardiac movement on inspection and palpation.

The thickened pericardium was incised and approximately 300 ml. of blood-stained fluid were obtained. There was a moderate amount of granulation tissue between the visceral and parietal layers of the pericardium. As the parietal pericardium was removed, there was little improvement in cardiac movement and it was apparent that the primary constrictor was the epicardium. The adherent, thickened visceral layer of the pericardium was then removed from the left side of the heart, the right ventricle, and part of the right atrium. With the release of the constricting epicardium there was immediate improvement in

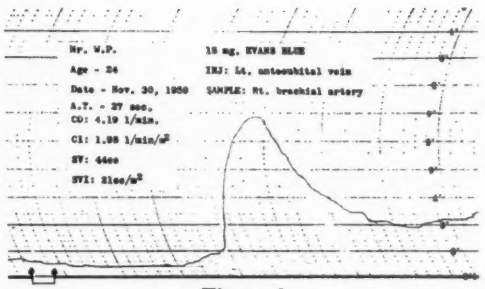

Figure 6

Cardiac-output estimation 8 weeks after the first study. The patient's heart rate, weight (183 lb.), and the oximeter settings were the same during each determination. Note the prolongation of appearance time and the marked drop in stroke volume index.

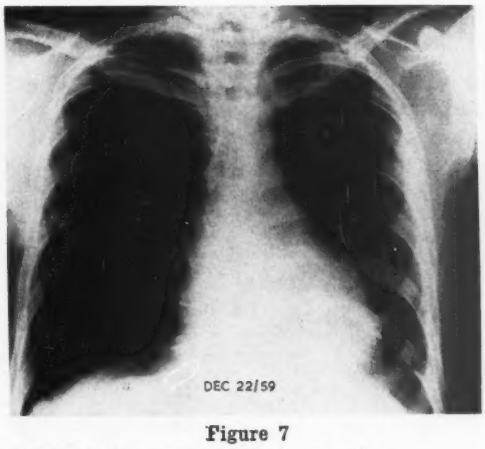

Figure 7

Postoperative x-ray, which is normal.

cardiac filling and function, and moderate dilatation occurred.

The postoperative course was uneventful. His pulse pressure, which preoperatively rarely exceeded 30 mm. Hg widened to 65 mm. Hg. The paradoxical pulsation and jugular venous distention disappeared. The pleural effusions and ascites cleared, and the liver was no longer palpable. He required no further diuretics, and the urinary sodium excretion became normal.

The chest x-ray (fig. 7) taken 2 weeks postoperatively was normal. The electrocardiogram showed deep inversion of precordial T waves.

The patient was discharged after 5½ months in the hospital, and on a follow-up visit in March 1960 he had no symptoms and examination was within normal limits.

Discussion

We have attempted to rule out any underlying disease process other than infectious mononucleosis that could have accounted for this patient's acute constrictive epicarditis. Thirteen smears and cultures and guinea pig inoculations from his pleural, pericardial, and ascitic fluid and from his sputum failed to show tubercle bacilli. Tuberculin tests have remained negative. Psittacosis has been ruled out by agglutination. Virus studies were made by inoculating sputum, throat washings, urine, stool, blood, pleural fluid, pericardial fluid, and pericardial tissue. No virus was isolated in over 13 passages in monkey kidneys and human amnion, chic embryo, and virus cultures. Lupus erythematosus cells were absent on repeated examinations from the peripheral blood and bone marrow. The pathologic report on the epicardium and pericardium, removed at operation, showed only chronic inflammatory tissue having no specific characteristics.

By March 1957, 12 cases of infectious mononucleosis with pericarditis had been reported. The review by Shugoli[5] stated that six of them had a friction rub, one a massive pericardial effusion, and the others only electrocardiographic evidence of acute pericarditis. Gardner[6] reported one case of acute pericarditis associated with infectious mononucleosis and Hutchinson[7] three cases.

Sixteen cases have been reported in the literature in which infectious mononucleosis alone seems to be the etiologic agent responsible for acute pericarditis. These cases are all well documented with clinical, electrocardiographic, and radiologic evidence of acute pericarditis; however, only two of these patients[4, 5] had massive pericardial effusions requiring pericardiocentesis. Our case is reported because it shows an interesting sequence of events: acute pericarditis followed by tamponade and constrictive epicarditis within 5 months of the onset of infectious mononucleosis.

Summary

The case history of a 24-year-old man is reviewed, who had pericarditis, cardiac tamponade, and many other manifestations of infectious mononucleosis. Cardiac-output estimations during the course of the illness showed a marked drop in his cardiac index. This, together with other findings, was interpreted as being due to the development of constrictive epicarditis. At operation the epicardium was densely adherent to the underlying myocardium. After extensive resection of both layers of the pericardium the patient made an uneventful recovery.

Acknowledgment

We wish to thank Dr. A. Rapoport, Director of the Metabolic Unit, Toronto Western Hospital, Toronto, for carrying out the metabolic studies in this case.

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Glycogen-Storage Disease

Report of a Case with Generalized Glycogenosis and Review of the Literature

By Otto F. Muller, M.D., Samuel Bellet, M.D., and Ali Ertrugrul, M.D.

THE PURPOSE of this presentation is to report in detail the clinical and pathologic findings of a case of generalized glycogen-storage disease involving the heart (type II). Because recent investigations have revealed additional data about the etiology and pathogenesis of this disease and because of the renewed interest in the subject, it seems timely to review its present status with particular reference to cardiac involvement.

Case Report

G. N. was a 6-pound, 6-ounce boy, born October 25, 1956, to a 26-year-old, gravida 7, para 6, white mother by normal spontaneous delivery after a normal gestation. During the first month of life the baby apparently was in good health and usually took its bottle feedings well, but failed to gain sufficient weight. In the second month, the legs swelled intermittently, and frequent bouts of abdominal distention and projectile vomiting occurred, usually 10 to 15 minutes following milk ingestion. The infant was constipated and had one well-formed yellow stool every 2 to 3 days. The mother of the infant was said to have had an enlarged heart. Unfortunately, both parents persistently refused clinical studies for themselves as well as for six living siblings.

On hospitalization at the age of 3 months the infant weighed 9 pounds, 5 ounces and appeared rather ill, hypoactive, dehydrated, and poorly nourished. Enlargement of the tongue was striking. The respirations were rapid. Dullness and absent breath sounds were elicited over the upper left chest and moist rales were present at both bases. The heart was considerably enlarged to the left by percussion, and tachycardia was present. The heart sounds were muffled and a soft (grade II) systolic murmur was heard with greatest intensity near the apex. The abdomen was distended and the liver palpable 2 to 3 cm. below the right costal margin. Bilateral grade-II pitting edema of the legs was noted. Roentgen study of the chest showed extreme globular enlargement of the heart and patchy pneumonic infiltrations in the left upper lobe, with secondary atelectasis in both upper and lower left lobes (fig. 1). Serial electrocardiograms revealed biventricular hypertrophy, sinus tachycardia, sinus arrhythmias, and nonspecific S-T and T-wave changes in all leads. Persistent Q waves were present in leads I, II, aV_L, and aV_F, and V_4 to V_6 (fig. 2). Blood electrolytes, peripheral blood picture, and urine were normal.

In the hospital the infant tolerated feedings well, and the pneumonia and cardiac failure responded promptly to antibiotics and digitalis. Because of the striking cardiac enlargement and the heart murmur the presence of a congenital cardiac anomaly was suspected. Two weeks after admission cardiac catheterization revealed normal right atrial and ventricular pressures and oxygen saturations. Following catheterization, the infant developed abdominal distention, respiratory distress, and the clinical findings of right lower lobe pneumonitis. After treatment with Digalen, prednisone, and oxygen, he improved gradually and compensation was restored in 3 weeks.

During the seventh month of life (the fourth month in the hospital), marked abdominal distention accompanied by fecal impactions frequently occurred and required enemas and almost daily digital removal.

In view of the clinical, roentgenologic, and electrocardiographic findings the possibility of myocardial storage disease was entertained, and a calf muscle biopsy was performed during the fifth month of hospitalization. Microscopic examination revealed loss of striation of the individual muscle fibers, with swelling and coarse vacuolization of the cytoplasm. Best's carmine stain showed that all these vacuoles were filled with glycogen. After the muscle biopsy several episodes of heart failure and pneumonia occurred, the infant remained almost constantly in critical condition. He died in congestive heart failure at the age of 8½ months.

At postmortem examination the weight of the body was 5,070 Gm. and the length was 60 cm. The abdomen was moderately distended. The heart was strikingly enlarged, almost entirely filling the left thorax. It weighed 170 Gm. (four and one-

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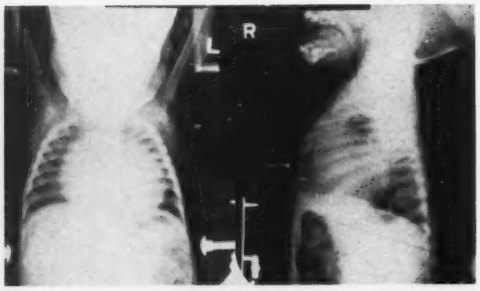

Figure 1

Posteroanterior and lateral films of the chest show marked enlargement and globular appearance of the cardiac silhouette, compression of the left lung, and pneumonic infiltration in the left upper lobe.

half times normal), and was globular in shape. The pericardial surface was firm, smooth, and pale pink in color. Both ventricular walls showed tremendous hypertrophy (the thickness of the right ventricular wall was 0.8 cm.; the left, 1.5 cm.) (fig. 3). The cut sections of the myocardium and the endocardium showed the same pale pinkish color as the epicardium. The tricuspid and mitral rings, the septa, and the great vessels were normal in size. The ductus arteriosus and foramen ovale were closed. Both lungs were partially atelectatic and the right lung showed small irregular grayish areas in a semi-firm reddish parenchyma. The spleen weighed 13 Gm. and appeared congested. The liver weighed 300 Gm. (normal 254 Gm.) and presented a smooth, regular, dark red surface. The cut sections revealed marked congestion. The two adrenal glands weighed 3.5 Gm. and the thymus weighed 4.5 Gm. The entire colon was markedly distended; the dilatation resembled that of Hirschsprung's disease.

The heart muscle was diffusely infiltrated with glycogen. Hematoxylin-eosin stains showed the typical "lacework" pattern; each fiber looked like a hollow cylinder surrounded by a thin delicate cytoplasm with the nucleus in the center of the cell (fig. 4). Best's carmine stain revealed that the hollow cylinders were filled with the red-staining glycogen (fig. 5). Even the smooth muscles of the coronary artery branches showed glycogen infiltration.

Glycogen accumulation was found in many other organs and tissues. The tongue was heavily loaded (fig. 6); the liver showed storage and congestion; and the renal cortex also contained some glycogen. The cells of Auerbach's plexus in the small and large intestine appeared foamy and swollen and also contained glycogen (fig. 7). Similar infiltration was observed in the sympathetic ganglia surrounding the adrenal glands. The lungs showed bronchopneumonia and atelectasis. There were no gross abnormalities of the brain, except that the tissue was unnaturally firm. The neuronal bodies throughout the specimen showed morphologic changes similar to those seen in amaurotic familial idiocy. The cell bodies were swollen and appeared either globular or pear-shaped. The nucleus was pushed to one pole; the Nissl substance of the cytoplasm was finely divided or absent except around the nucleus. In addition, one or more vacuoles were present. This change was marked in all cell groups in the pons and medulla and in the anterior horns of the cervical cord (figs. 8 and 9). It was conspicuous in the pallidum, subthalamic body, and substantia nigra, but less well marked in the putamen, red nucleus, and thalamus. Both periodic acid-Schiff and Best carmine stains gave an intensely positive reaction for glycogen within the cells of these areas. Similar material was found in the perivascular spaces, the muscularis of arteries, and in the entire ependymal lining of the ventricles. There was diffuse scattering of the stained material throughout the entire brain substance. It appeared as a fine granular substance in the white matter. It was also present in the cerebral cortex and was only sparsely seen in the granular and molecular layers of the cerebellum. These changes were absent from the brains of other infants of the same age. The final diagnoses were glycogen-storage disease (Cori-type II); pneumonia and atelectasis; and megacolon (Hirschsprung's disease). The immediate cause of death was cardiac failure.

Review of the Literature

The history of diseases with abnormal storage of glycogen dates back to 1928, when Snapper and van Crefeld[1] described an infant with hepatomegaly, hypoglycemia, and acetonemia. One year later von Gierke[2] reported his anatomic-pathologic investigations of the accumulation of glycogen in liver and kidney cortex and introduced the term hepatonephromegalia glycogenica for this disease. During the following years single cases were reported in which the glycogen storage in the liver was associated with cirrhosis.[3, 4] Others exhibited the clinical picture of amyotonia congenita and of myxedema.[5, 6, 7]

The first to describe glycogen storage in the heart muscle was Pompe in 1932,[8, 9] as a result of histochemical studies in a case of idiopathic hypertrophy of the heart. Although he found glycogen in the liver, kidney, thyroid, spleen, and striated muscle, he called this dis-

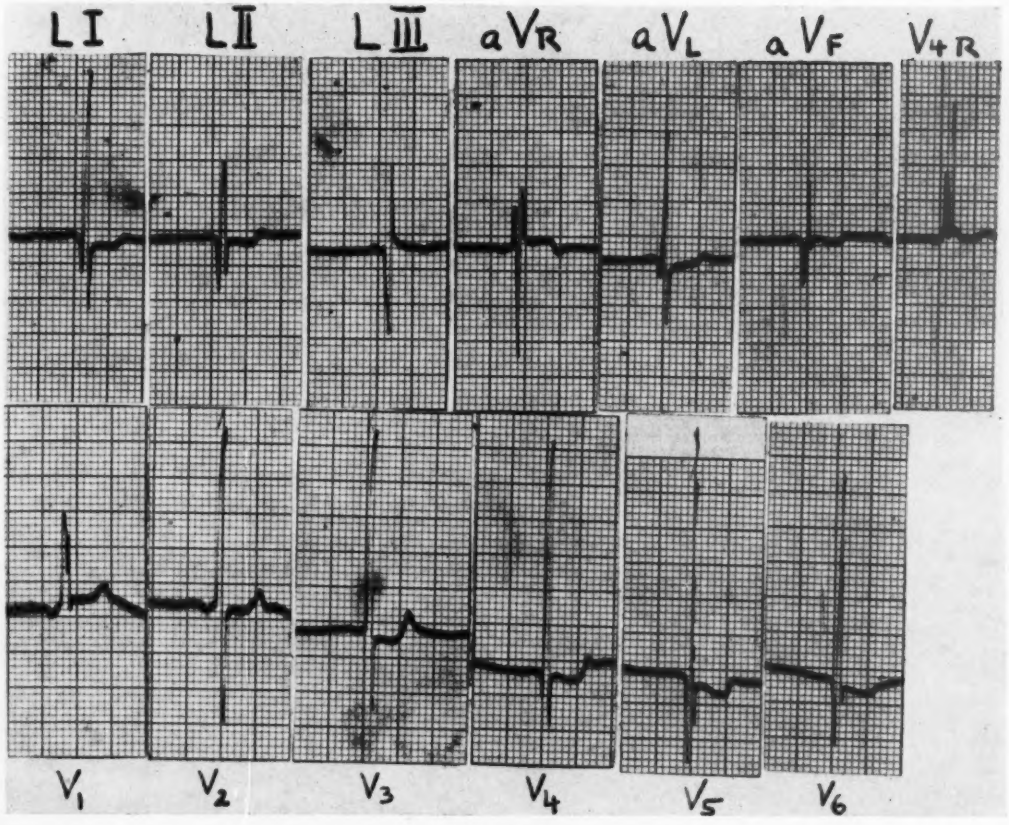

Figure 2

Electrocardiogram showing Q waves in leads I, II, aV_L, aV_F, V_4 to V_6, and nonspecific S-T and T changes in all leads.

ease "cardiomegalia glycogenica." It soon became apparent that all these cases were variants of a disturbance in carbohydrate metabolism manifested by storage or excessive amounts of glycogen in the tissues.[10–13] Initially, it was suggested that the cause of the defect resulting in glycogen storage was most probably a deficiency of enzymes involved in the breakdown of glycogen.[10, 12, 14] This theory was verified in 1952 by Cori and Cori, who reported a case of liver glycogenosis with deficiency of glucose 6-phosphatase.[15, 16] With improvement in biochemical methods, various classifications of this syndrome were presented, which apparently depended upon the clinical, pathologic, or biochemical orientation of the author.[7, 17–22] In addition to deficiency of various enzymes, the chemical structure of the glycogen molecule itself was shown to be important in the pathogenesis.

According to the recent classification of Cori and Andersen[16, 23, 24] four different types may be distinguished (types I, II, III, and IV).

Type I represents the original von Gierke disease with accumulation of normal glycogen molecules in the liver and kidney cortex. Clinically, the infants manifest growth retardation as displayed by a small body size with "doll-like" features, a protruding abdomen with a strikingly enlarged liver, but without splenomegaly. The kidneys are, at times, greatly enlarged. Anorexia, vomiting, and weight loss as well as convulsions and coma

Figure 3

Gross appearance of heart and lungs. The heart was sectioned along the interventricular septum to show both left and right ventricular walls. Atelectasis of the left lung as a result of the compressive effect of the heart is clearly discernible.

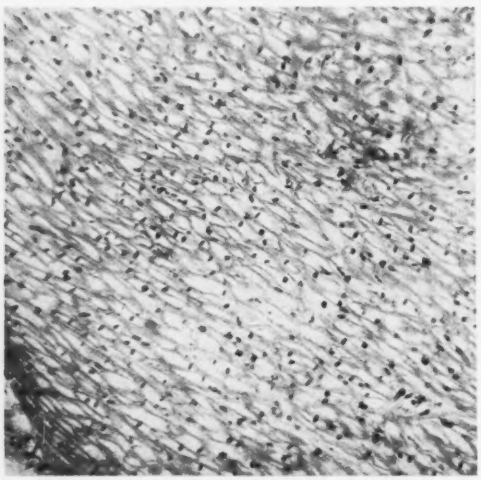

Figure 4

A medium-power view of the myocardium shows a "lacework" appearance. Hematoxylin-eosin stain.

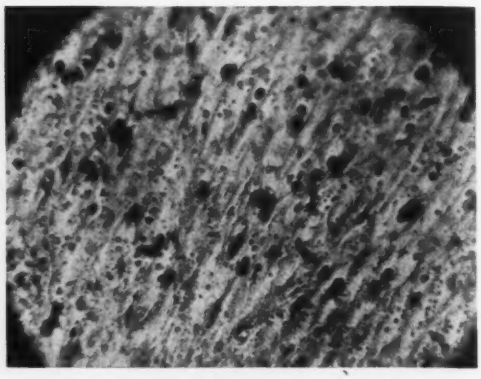

Figure 5

In a high-power view the hollow myocardial fiber cylinders of the myocardium are seen to contain red-staining glycogen droplets. Best's carmine stain.

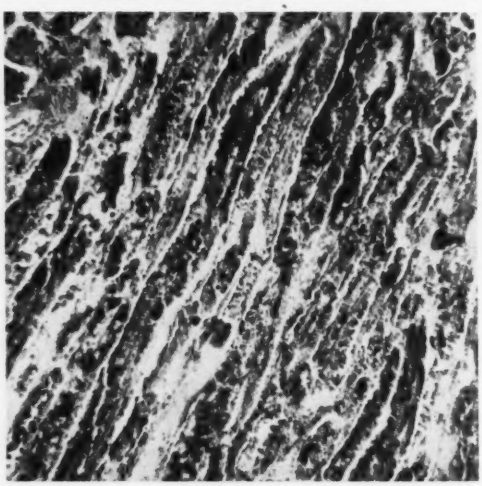

Figure 6

Tongue: The striation of skeletal muscle is easily discernible as is the accumulation of glycogen within the muscle fibers. (The dark material is the red-staining glycogen). Best's carmine stain.

have been observed. Laboratory studies show hypoglycemia, hyperlipemia, hypercholesteremia, increased blood glycogen levels, acidosis, and acetonuria. These subjects manifest a diminished response to epinephrine, impaired glucose tolerance, hypersensitivity to insulin, decreased or absent neutral serum phosphatase, inadequate response to glucagon and rise in α- and β-globulin in the serum with aminoaciduria.[25] Chemical analysis of the liver at necropsy reveals an almost complete absence of one enzyme, glucose 6-phosphatase. Death usually occurs from intercurrent infections.

Type II shows generalized glycogenosis with considerable accumulation of normally structured glycogen in all tissues that normally contain glycogen. The heart is usually extensively involved, as in the cases of Pompe.[8] St. Agnese et al.[26,27] reviewed the findings in 14 cases of cardiac glycogen storage, and

Rossi,[28] in seven. Since one of the five cases of Illingworth[29,30] showed an abnormal glycogen molecule, it would not fall in type II. Two cases of cardiac glycogen storage in siblings were described by Childs et al.[31] Several cases with neuromuscular glycogen storage showed markedly enlarged hearts and abnormal electrocardiograms.[7,31,32] Recently, one case of cardiac storage with hepatic, renal, and bladder involvement was added by Mazzitello and Briggs.[33] The glycogen displaces the muscle bundles of the myocardium with the result that heart failure is a common cause of death. This type was therefore often referred to as cardiomegalia glycogenica.[8,9] It should again be emphasized, however, that this is a generalized glycogenosis, and the stored glycogen may be found in all tissues where it is usually present. The tongue, for instance, was found to store glycogen up to 15 per cent of its total weight, a finding that occasionally led to an incorrect diagnosis of myxedema.[7] The liver may contain up to 10 per cent and the kidney cortex is often markedly involved. The underlying mechanism of glycogen storage of this type has not been determined. According to present knowledge, the glycogen has a normal structure and an enzyme deficiency has not been detected; glucose 6-phosphatase is within normal limits.

Type III, originally described by Cori[16] in 1952, was diagnosed by analysis of liver and muscle in a 12-year-old child. The glycogen accumulates chiefly in skeletal muscle, heart, liver, kidneys, and to a lesser degree in other tissues. These subjects present a large liver, flaccid muscles, and at times, an enlarged heart. The debrancher enzyme (amylo-1, 6-glucosidase) is absent in skeletal and heart muscle.[30] The glycogen molecule is abnormal, having very short outer branches and approaching the structure of phosphorylase limit dextrin. The abnormality may be the result of the deficiency of the debrancher enzyme. Cori has shown that this type of glycogen storage is a familial disease that is apparently as common as the original von Gierke's disease, but the mortality is much lower.

Type IV also shows storage of abnormal glycogen molecules in the liver, reticuloendothelial system, and probably skeletal muscle. The literature includes only one case that has been studied clinically, pathologically, and biochemically.[13,16,24,34] This infant showed hepatomegaly, splenomegaly, hypoglycemia, and icterus. The postmortem examination revealed glycogen storage in a severely cirrhotic liver and in the spleen, lymph nodes, and intestinal mucosa. It was determined by biochemical analysis that the glycogen molecule has fewer and longer chains than its normal counterpart and resembles the structure of maize amylopectin. The storage of these molecules is associated with cirrhosis of the surrounding tissues. The glycogen is probably so insoluble that it comes out of solution at 37 C., acts as a foreign body, and gives rise to fibrous tissue reactions. The chemical structure suggests a deficiency in the branching enzyme (1, 4→1, 6-transglucosidase).[16,29,35] It has been shown that this disease also is familial.[16,23,24]

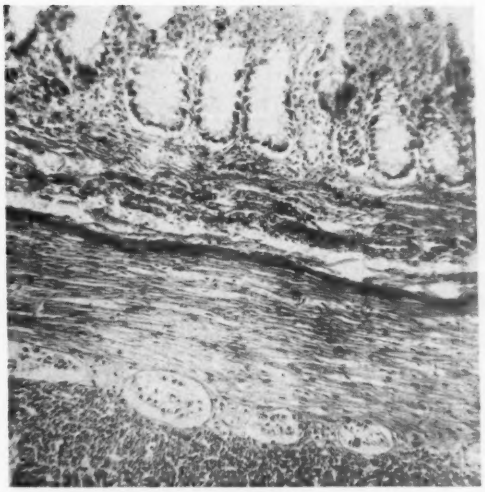

Figure 7

Intestine: Note the foamy and swollen cells of Auerbach's plexus. Hematoxylin-eosin stain. Best's carmine stain revealed heavy glycogen storage in these cells (bottom of picture).

A type V with glycogen storage in striate muscle mainly has been proposed,[36] but there is very little information available and complete studies have not been reported thus far.

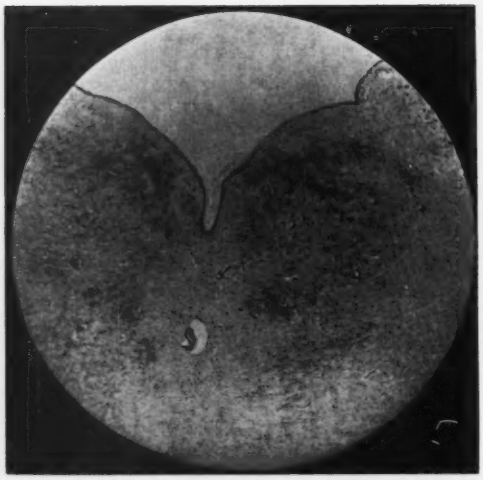

Figure 8

Low-power view of the intensely positive glycogen reaction in the nuclei of the dorsal vagus (superior) and hypoglosus (inferior) nerves on the floor of the fourth ventricle. Periodic acid-Schiff stain.

Figure 9

High-power view of the glycogen-positive reaction in the nuclei at the base of the pons. Periodic acid-Schiff stain.

Discussion

According to the criteria recently established, our case is classified as type II glycogen-storage disease, accompanied by unusual involvement of the nervous system. Infants with this type tolerate their feedings poorly, fail to gain weight, show progressive anorexia and vomiting, and are subject to attacks of dyspnea, cyanosis, and cardiac failure. They are listless, may exhibit muscular weakness, neurologic abnormalities, and striking enlargement of the tongue.[37] The symptoms usually start between the second and sixth month of life. In our case the feeding problems associated with constipation and projectile vomiting led to hospitalization, but no satisfactory reason for the feeding problems was found. Necropsy findings suggest that the vomiting was probably the result of the megacolon (Hirschsprung's disease) caused by the abnormality of the intramural plexus myentericus (Auerbach), which showed extensive glycogen storage. We are not aware of other reports in which feeding problems and constipation were correlated with glycogen storage in the autonomic ganglia cells of the intestine. The infant subsequently developed pneumonitis and atelectasis of the lungs and frequent bouts of cardiac failure.

Probably the most prominent physical finding was the enormous enlargement of the heart, which nearly filled the left thoracic cavity. A variety of cardiac murmurs has been described, but a systolic murmur appears to be predominant.[27, 31, 33] High voltage with ST-T changes similar to those in our case have been observed in other cases of cardiac glycogen-storage disease.[27]

The carbohydrate metabolism in glycogen-storage disease is usually within the normal limits; there is no acidosis, ketosis, or hypercholesteremia.

The prognosis of type II glycogen-storage disease is very poor. With the typical criteria the disease is practically always fatal during the first 8 months of life. About 20 cases have been reported thus far in the literature. We as yet have no definite information whether milder cases may survive for longer periods.

A skeletal muscle biopsy, as in our case, may establish the diagnosis. It has not been definitely established whether glycogen is always stored in the skeletal muscle of these patients. Eight of the 14 cases of St. Agnese[27] and two of Rossi's seven[28] showed storage in

the skeletal muscle, but it is not known whether a muscle biopsy was performed in all cases.

A positive muscle biopsy in infants with large globular hearts and cardiac failure without evidence of congenital valvular or septal defects is suggestive of type II glycogen-storage disease. The differential diagnosis includes hypothyroidism, mongolism, amyotonia congenita, idiopathic myocarditis (Fiedler), endocardial fibroelastosis, and fat myocarditis (Kugel-Stologg).

The pathologic findings include a five- to six-fold increase in the weight of the heart, a lacework appearance of the myocardial fibers with enormous accumulation of glycogen within the fibers replacing the muscular tissue. Glycogen can be found also in the tongue, in the musculature of the diaphragm, neck, trunk, and extremities, in smooth muscle, in the reticuloendothelial system, kidney, liver, bone marrow, thymus, and in the central nervous system and autonomic ganglia.

Summary

A case of glycogen-storage disease (Cori type II), with accumulation of glycogen in the myocardium, skeletal muscle, smooth muscle, liver, kidney, central nervous system, and autonomic ganglia is presented.

Glycogen storage in the autonomic ganglia of the intestinal tract (Plexus-myentericus-Auerbach), which gave rise clinically to Hirschsprung's disease, could explain the feeding problems and constipation often observed in these cases.

The classification into four different types of Cori and Andersen appears to be the most satisfactory one at the present time. These types are different disease entities with the same expression of abnormality, the deposition of glycogen; but the pathogenesis and the clinical and pathologic findings are strikingly different.

Glycogen storage of the heart is probably more common than the review of the literature indicates. Many of these cases are missed, mainly types III and IV, because the possibility is not considered and the patient is inadequately studied in life and during necropsy.

Acknowledgment

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When listening to heart murmurs you must tune up your auditory hair cells and flatten out your Pacinian corpuscles.—Sir William Osler. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 100.

An Angiocardiographic Sign of Aortic Regurgitation

Its Utilization for the Measurement of Regurgitant Flow

By Rene A. Arcilla, M.D., Magnus H. Agustsson, M.D., Zwi Steiger, M.D., and Benjamin M. Gasul, M.D.

FOLLOWING the recent advances in cardiovascular surgery, the quantitation of abnormal hemodynamics has assumed paramount importance to clinicians and surgeons alike, and has been a constant challenge to research workers. The quantitative estimation of the severity of aortic insufficiency, for example, is still an unsolved problem. The different dye-indicator studies[1-6] and the technic of venous occlusion plethysmography introduced by Mackay[7] are examples of efforts to solve this problem.

We wish to describe a technic of retrograde aortography done on five patients with aortic insufficiency and on five patients without this valvular defect. The aortograms demonstrate the movements of the opacified column of blood in the aorta, forward with ventricular systole and backward with diastole. While this phenomenon is a well-known hemodynamic assumption, it has not been demonstrated previously by contrast radiography. This paper deals with a description of the aortograms and their hemodynamic significance and with a presentation of a method for the estimation of the volume of regurgitant flow.

Materials and Methods

Ten patients were studied in this series; seven male and three female, and their ages ranged between 3 months and 19 years. Five had clinical findings of aortic insufficiency consisting of a wide pulse pressure, a hyperdynamic apical impulse, an accentuated aortic closure sound, and an early decrescendo blowing diastolic murmur over the aortic and left lower parasternal areas. The chest roentgenograms and electrocardiograms demonstrated left ventricular hypertrophy. The brachial arterial pulse tracings also showed the usual findings of aortic insufficiency. Two cases had associated mitral regurgitation, whereas the rest had isolated aortic insufficiency. The etiology of the valvular lesions was rheumatic fever. None of the patients was in congestive heart failure.

Retrograde aortography was performed on each of the 10 patients. In the five patients without clinical and laboratory evidence of aortic insufficiency it was performed to investigate some other extracardiac disorder. The method consisted of inserting a Lehman catheter of the widest diameter possible through an arteriotomy in the left brachial artery. The catheter was advanced under fluoroscopic guidance until its tip was in the descending aorta at least two inches below the arch. Ninety per cent aqueous solution of Hypaque sodium was injected rapidly in a dose of 0.7 to 1.0 ml. per Kg. of body weight. At the end of the procedure, the arteriotomy was repaired.

The angiocardiograms were obtained by means of an Elema angiocardiographic apparatus with an exposure time of 1/30 or 1/60 second, 8 radiograms per second being taken simultaneously in two planes. These were analyzed in detail, with special attention to the changing position of the opacified column of blood and to the diameter of the aorta during the various phases of the cardiac cycle. The stroke volume and the amount of aortic regurgitation were also calculated. In order to derive the actual size of the aorta from its apparent size in the aortogram, a standard correction curve for the magnification in the angiocardiogram was prepared from a plot of the per cent magnification of metallic rings of varying sizes at varying distances from the film and with a constant tube-to-film distance of 36 inches (fig. 1). These observations were made in both planes of the Elema angiocardiographic apparatus. Of the many factors producing image amplification, the object-to-film distance is practically the only one that needed correction in our study, since the angiocardiographic apparatus used had a fixed focal aperture, a fixed focal-film distance of 36 inches, and a fixed position and angulation of the tube in reference to the film.

The angiocardiograms were performed with the patient in the recumbent position. In every case, just prior to the injection of the contrast sub-

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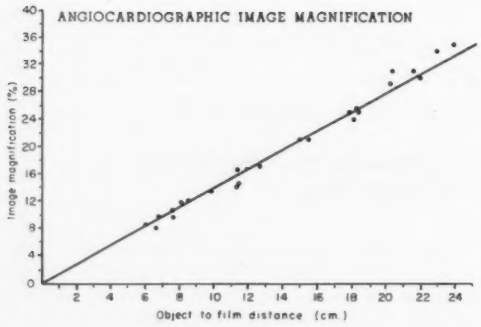


Figure 1

Relationship of angiocardiographic image magnification (expressed as per cent of the actual object size) to the object-to-film distance.

stance, the anteroposterior and transverse diameters of the chest and the distance of the midsternum from the lateral grid were accurately measured (fig. 2). The sagittal and transverse diameters of the chest in the aortograms were similarly measured. The distance from the midpoint of the descending aorta to the lateral chest wall (h) and to the posterior chest wall (I) were also determined from the aortograms. The true aorta-film distances in the anteroposterior and in the lateral planes were derived* and radiographic magnification of the aorta in either plane was determined from the standard correction curve (fig. 1).

Results

Aortographic Findings

The abnormal pulsatile flow in aortic insufficiency is clearly demonstrated in the aortogram (fig. 3). The opacified column of

*To determine the aorta-to-film distance (fig. 2).

(a) In anteroposterior projection

$$O_a = \frac{I}{C'D'} \cdot CD$$

$$O_f = O_a + y$$

(b) In lateral projection

$$O_l = \left(\frac{h}{A'B'} \cdot AB\right) + g$$

$$O_f = O_l + y$$

O_a = aorta-to-grid distance in anteroposterior projection

O_f = aorta-to-film distance

O_l = aorta-to-grid distance in lateral projection

O_f = aorta-to-film distance

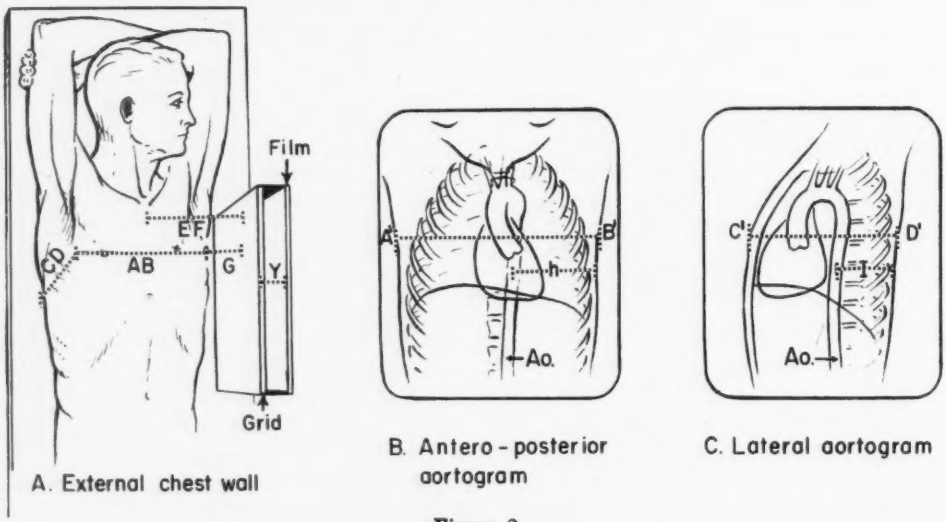


Figure 2

Landmarks in the chest and in the aortograms for deriving the true aorta-to-film distance. One grid is adjacent to the left chest wall and the other is under the patient's back. AB, lateral diameter of chest; CD, anteroposterior diameter of chest; A'B', lateral diameter of chest in the frontal aortogram; C'D', anteroposterior diameter of chest in the lateral aortogram; EF, distance from midsternum to grid; G, distance from left chest wall to grid; Y, distance from grid to film (constant); h, distance from descending aorta to left lateral chest wall in the frontal aortogram; I, distance from descending aorta to posterior chest wall in the lateral aortogram.

Table 1

Data on Estimated Stroke Volume and Regurgitant Volume on Five Patients with Aortic Insufficiency

Patient	Valvular defect*	Age (yrs.)	BSA ($M.^2$)	Diameter of aorta (cm.) systole†	diastole‡	$\frac{S-D}{D} \times 100$	Stroke volume (SV) (ml./$M.^2$)	Regurgitant volume (RV) (ml./$M.^2$)	$\frac{RV}{SV} \times 100$ (%)
1	AR	12	1.30	1.7	1.3	31%	42	29	69
2	AR	19	1.75	2.6	1.9	37%	54	40	74
3	AR	11	1.35	1.9	1.5	27%	50	32	64
4	AR; MR	9	1.10	1.7	1.5	13%	37	16	43
5	AR; MR	17	1.40	2.3	2.0	15%	54	33	61

*AR, aortic regurgitation; MR, mitral regurgitation.
†Maximal diameter.
‡Minimal diameter.

blood moves distally during ventricular systole and backward during ventricular diastole, the extent of the movements being indicated by the changing position of the peripheral zone of the contrast substance. This to-and-fro movement of the opacified column of blood is noticeable at the proximal portion of the descending arch and of the arch during several cardiac cycles. The aortogram also demonstrates the abnormal expansile movements of the aorta. Dilatation of the aorta occurs immediately during the early phase of ventricular systole (fig. 3A and 3F), followed later by a striking reduction in its size with the centripetal movement of the radiopaque material during diastole (fig. 3C to 3E).

In the other 5 patients without evidence of aortic insufficiency, the centripetal movement of the opacified column of blood during diastole was not observed. The differences in the aortic diameters during systole and during diastole expressed by the fraction,

$$\frac{\text{diameter systole-diameter diastole}}{\text{diameter diastole}}$$

were also not so much as in those with aortic insufficiency. The higher values noted in the latter group obviously reflected the greater stroke volume and also the considerable reduction in the aortic diameter during diastole as a result of the aortic reflux into the left ventricle.

Estimation of Stroke Volume and Regurgitant Volume

The forward movement of blood in any segment of the aorta during systole is due to the thrust imparted on the residual contents in the ascending aorta by the ventricular stroke volume. The extent of this forward displacement in any segment of the descending aorta indirectly indicates the stroke volume that has bypassed the brachiocephalic vessels. In aortic insufficiency the extent of the centripetal movement of blood in the arch and descending aorta similarly reflects the volume of regurgitation from the descending aorta into the left ventricle during diastole. With our method the stroke volume is determined from the volume of the displaced contrast material following systole; the regurgitant volume is derived from the magnitude of the centripetal return of the opacified blood during diastole. The accuracy of the estimated stroke volume and regurgitant volume depends on how clearly defined these forward and centripetal movements are depicted in the aortogram. This, in turn, depends on how clearly outlined is the zone of demarcation between the dye-containing and the non-dye-containing blood columns in the aorta.

The difficulty in calculating the volume of any segment of the aorta, as seen in the aortograms, may be resolved by assuming that the aorta is a long, imperfect cylinder with its distal end smaller than its proximal portion in a gradually tapering fashion. Its proximal segment is arched, whereas its distal segment is straight (fig. 4). With a planimeter the surface area of any portion of the aorta in the aortogram can be measured.

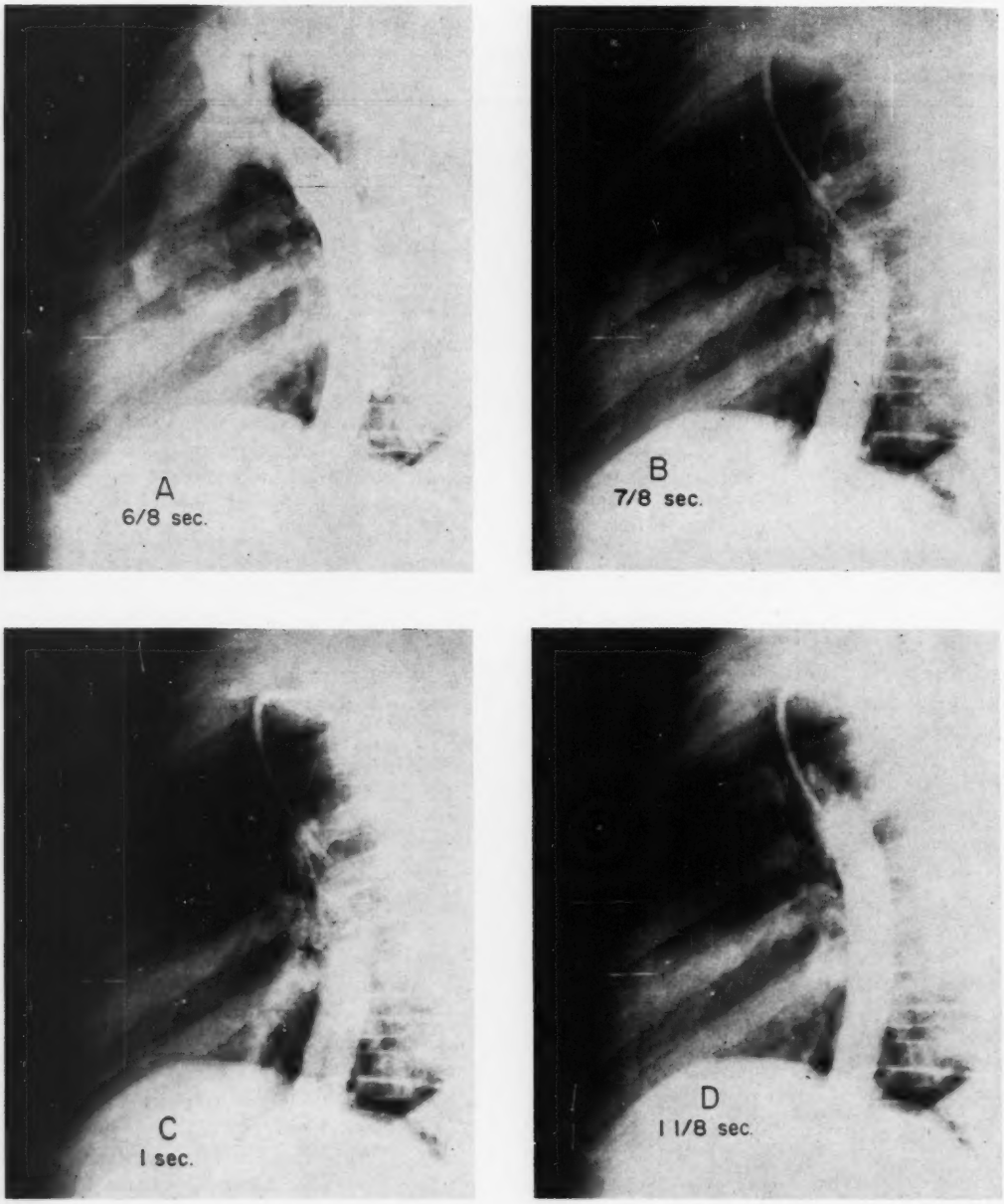
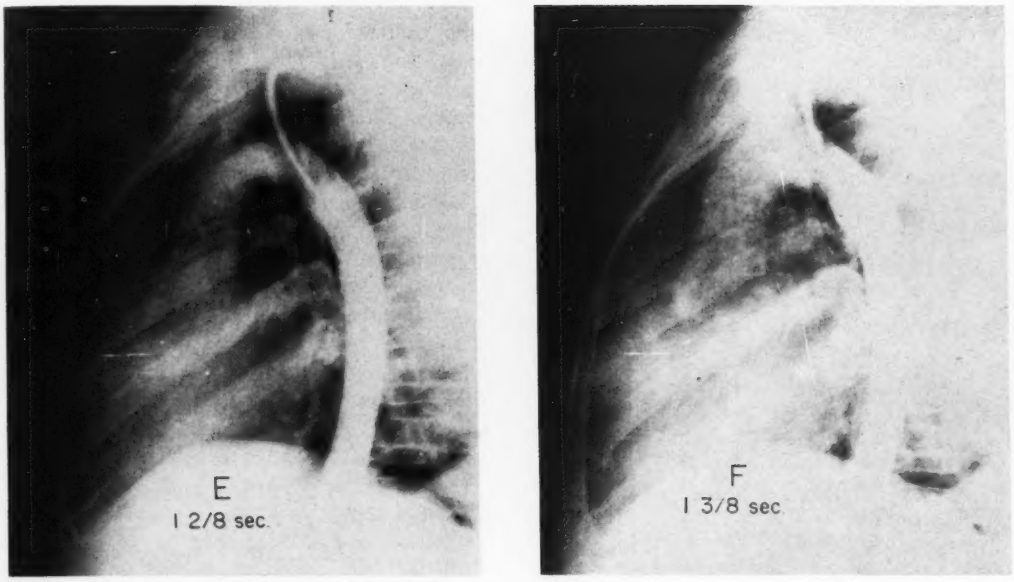


Figure 3

Aortogram in case 1 demonstrating the to-and-fro movement of the opacified vascular column and the prominent expansile movements of the aorta. A, B, and C demonstrate the foreward movement of the column during systole; C, D, and E demonstrate the backward movement of the same column of blood during diastole. F illustrates the sudden increase in the aortic diameter with the onset of systole. Arrows indicate the approximate level of the contrast substance.



By dividing this area by the average diameter of the segment, the length of a rectangle with the same surface area is obtained. From the average diameter of the aortic segment, the mean circular area of the aorta is also derived. By multiplying this area by the "corrected" length of the aortic segment, (which is equivalent to the length of the theoretical rectangle), the volume of the aortic segment is obtained.*

*To determine the volume of an aortic segment (fig. 4).

(a) Average diameter of aortic segment (D_a)

$$D_a = \frac{D_1 + D_2 + D_3 + D_4 + D_n}{4 + n}$$

(b) "Corrected" length of aortic segment (L_a)

A_a (determined planimetrically) $= A_b$

$$L_a = L_b = \frac{A_a \text{ (or } A_b)}{D_a \text{ (or } W_b)}$$

(c) Volume of aortic segment (V_a)

$$V = \pi r^2 l$$

in which V = volume of any cylinder

in which r = radius of cylinder

in which l = length of cylinder

This equation may be used to determine volume of any aortic segment:

$$V_a = \pi \left(\frac{D_a}{2}\right)^2 \cdot L_a$$

$$= 0.7854\ D_a^2 \cdot L_b$$

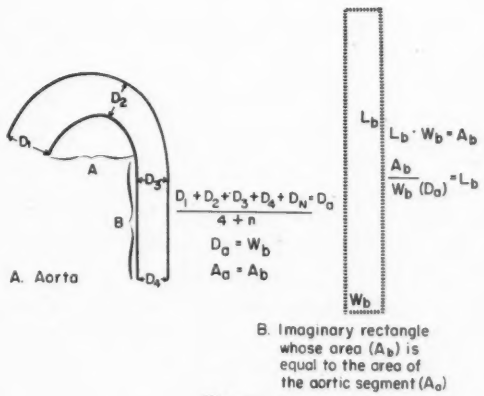


Figure 4

Diagram of a segment of the ascending aorta and descending aorta whose area is equivalent to that of the rectangle on the right. The arched segment (A) represents the ascending and arch; the straight segment (B) represents the descending aorta. D_1, D_2, D_3, D_4, D_n = diameters of aorta at various levels; D_a = average diameter of aorta at segment; A_a = area of aortic segment; A_b = area of rectangle; L_b = length of rectangle; W_b = width of rectangle.

As demonstrated in figure 5, the distal border of the stroke volume at the end of ventricular systole would assume a lower level

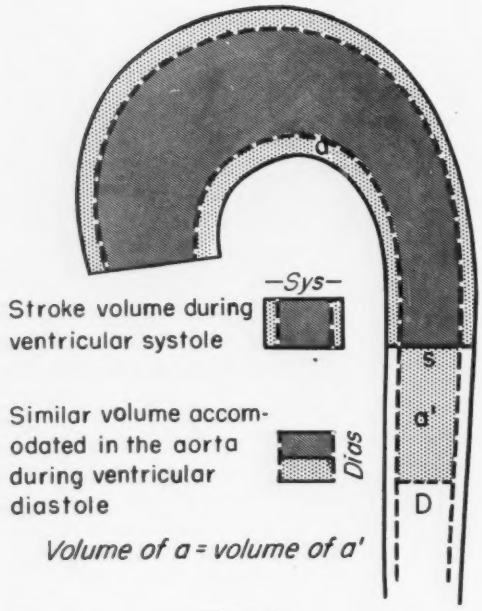


Figure 5

Diagram of the ascending and descending aorta illustrating the effect of aortic expansion on the distal level of the stroke volume (S). In diastole when the aortic diameter is narrower (dotted lines), the inferior level of an equivalent volume would be more distal (D). Thus the additional volume of the aorta (a) resulting from its dilatation during systole is equivalent to the volume of the descending aorta during diastole (a') confined between the distal level of the stroke volume during systole (S) and that of a similar volume during diastole (D).

if this volume were accommodated in the same aortic segment during diastole when its diameter is narrower. These two levels, the actual and the theoretical "diastolic" levels, demarcate a segment of the descending aorta (a') whose volume during diastole is equal to the additional volume of expansion of the aorta during ventricular systole (a). This volume between the two levels is, therefore, equivalent to the value obtained by multiplying the stroke volume by the per cent of aortic dilatation during systole ($\frac{S\text{-}D}{D} \times 100$ = per cent; in which S = diameter during systole and D = diameter during diastole). These considerations are important in calculating the volume of aortic regurgitation.* Unless this correction factor is utilized, the calculated regurgitant volume is likely to be underestimated, since the initial level of the dye at the end of systole (or the beginning of diastole) should have been theoretically lower. It should be pointed out that this corrected volume does not represent the absolute aortic regurgitant volume, since the method does not estimate the volume of blood from the brachiocephalic vessels similarly regurgitated into the left ventricle. When expressed, however, as a per cent of the stroke volume, it becomes more accurate and meaningful, since the stroke volume, calculated by this method, also does not take into consideration the amount of blood that goes to the brachiocephalic vessels.

Discussion

Since Corrigan's original description of the characteristic bounding pulse in aortic insufficiency,[8] numerous studies on the circulatory hemodynamics in this entity have been reported. Retrograde aortography performed with the injection of the contrast substance into the ascending aorta has been described by Wilder et al.[9] They have shown that aortic reflux into the left ventricle occurs only when aortic insufficiency is present. While this method clearly demonstrates the regurgitant stream, it cannot quantitate the amount of aortic regurgitation.

The movements of the opacified column

*To "correct" the estimated volume of aortic regurgitation (fig. 5).

(a) Volume expansion of aorta during systole (V_e)

$\frac{S - D}{D} \cdot 100$ % increase in aortic diameter during systole

in which S = diameter of aorta during systole
D = diameter of aorta during diastole

$$V_e = SV \cdot \left(\frac{S - D}{D} \cdot 100\right)$$

in which SV = stroke volume

(b) "Corrected" volume of aortic regurgitation (V_c)

$$V_c = V_u + V_e$$

in which V_u = estimated volume of regurgitation
V_e = volume of expansion during systole
V_c = "corrected" volume of aortic regurgitation

of blood in the aorta, as demonstrated in our aortograms, confirm the well-established abnormal pulsatile flow in aortic insufficiency derived from studies on central and peripheral pressure pulse curves, electrokymograms, ballistocardiograms, and recently from indicator-dilution methods.[1-6] The aortograms also demonstrate why effective systemic circulation time may be unusually prolonged, especially when the regurgitant volume closely approximates the stroke volume. In this condition a large portion of the systolic output remains in the proximal aorta for a longer time, because of its to-and-fro movement during ventricular systole and diastole.

The striking diminution in the diameter of the aorta simultaneously with the centripetal movement of the blood column refutes Stewart's original concept that the reflux volume in aortic insufficiency is small, and that the collapse of the pulse is due to reflex vasodilatation of the systemic vessels.[10] Rather, it illustrates Wigger's contention, which is well accepted today, that the abnormal fall in the diastolic pressure is due to the regurgitation.[11] These abnormal expansile movements of the aorta illustrate the typical water-hammer pulse in this entity. We do not need to take into account the possible influence of atherosclerosis on aortic distensibility in our group of patients.

The volume of regurgitation in aortic insufficiency has long been a matter of speculation. Stewart[10] and later Wiggers and Green[12] assumed only a small regurgitant volume; Lewis and Drury[13] believed that as much as 50 per cent of the stroke volume may be lost in the regurgitant flow. Other investigators [1-5, 14, 15] have suggested that the regurgitant volume may be equal to, or may even exceed the stroke volume. Although flowmeters have been successfully utilized in experimental studies, their clinical use in man is not feasible. The dye-dilution technics described by Warner and Toronto[2] and by Braunwald and Morrow[1] are based on the same principle. They consist essentially of injecting a dye-indicator substance at various levels of the descending aorta and simultaneously determining the dye concentration in the femoral artery and left radial artery,[2] or in the right ear lobe by means of continuously recording oximeters.[1] In the absence of aortic insufficiency, the dye is not detected in the radial artery or at the ear lobe during its primary circulation as long as the site of injection is below the level of the arch. In aortic insufficiency the lowest level in the descending aorta, from which the indicator substance is recovered into the brachiocephalic vessels, represents the inferior level of the blood column that returns centrally into the arch or ascending aorta during diastole. With varying degrees of aortic regurgitation, these levels also vary. The volume of aortic regurgitation that represents a fraction of the total aortic compartment is derived from the estimated total aortic volume. The indicator-dilution methods described by Korner and Shillingford[3, 4] and by Lange and Hecht[5] determine the ratio of the regurgitant to the nonregurgitant flow from the simultaneous pulmonary artery and systemic artery dye curves following peripheral venous injection of dye. The other method reported by Brotmacher et al.[6] involves the injection of a dye into the ascending aorta, and recording simultaneous dye curves obtained from the left ventricle and from the femoral artery.

Our technic of retrograde aortography was designed basically on the same principle as the previous two dye-dilution methods.[1, 2] It also involves calculating the volume of the aortic segment that the radiopaque substance traverses as it returns centrally to the arch or ascending aorta during diastole. It has the advantage of permitting the determination of the physiologic size and volume of the aorta at the time of the test. It also makes possible the estimation of the left ventricular stroke output, so that the degree of aortic regurgitation can be expressed as a fraction of the stroke volume. This is more accurate than expressing the regurgitation volumetrically alone, since in the determination of both the stroke volume and the quantity of aortic regurgitation, the volume of blood passing through the brachiocephalic vessels is not

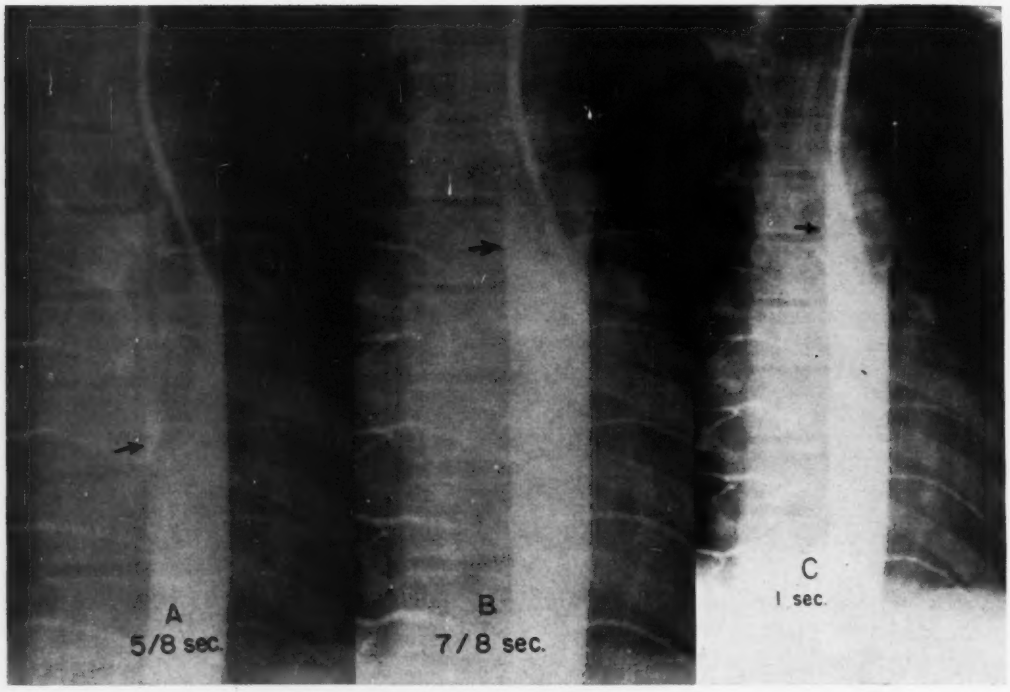


Figure 6a

Aortograms of a patient without aortic insufficiency demonstrating the "pseudocentripetal" movement of blood during diastole while the contrast substance is still being injected. During systole the contrast substance moves distally (A). During diastole the contrast substance opacifies the vascular column close to the site of injection giving an impression of a centripetal movement (B, C).

considered. Since both determinations are calculated by the same method, any error inherent in the method is reflected in both values.

The method is not devoid of difficulties and sources of error. The peripheral border or edge of the opacified column (see arrows, figs. 3 and 6) is not always distinctly outlined, especially at the beginning of systole when dispersal of the contrast material at the demarcation zone by forces other than those under study occurs. This difficulty is obviated if the contrast substance is injected rapidly into the descending aorta, for which reason the catheter with the widest diameter that can be accommodated in the exposed brachial artery is desirable. An arteriotomy is necessary that must be repaired at the end of the procedure. Since the aortograms are taken at a speed of 8 radiograms per second, the border of the contrast substance in *late* systole, as viewed in the film immediately preceding the picture demonstrating early centripetal movement, would not be at the same level were the picture taken at the *end* of systole. The same difficulty is encountered in determining the level of the contrast substance at the *end* of diastole. The identification of these nondiscernible vascular movements, which occur within the last 0.09 to 0.10 second (time interval between two successive frames) of systole and diastole, is obviously essential for more accurate estimation of the stroke volume and the regurgitant volume. Cineangiocardiography should eradicate this difficulty. On the other hand, the delineation of the borders of the contrast substance may not be so distinct as in the serial aortograms.

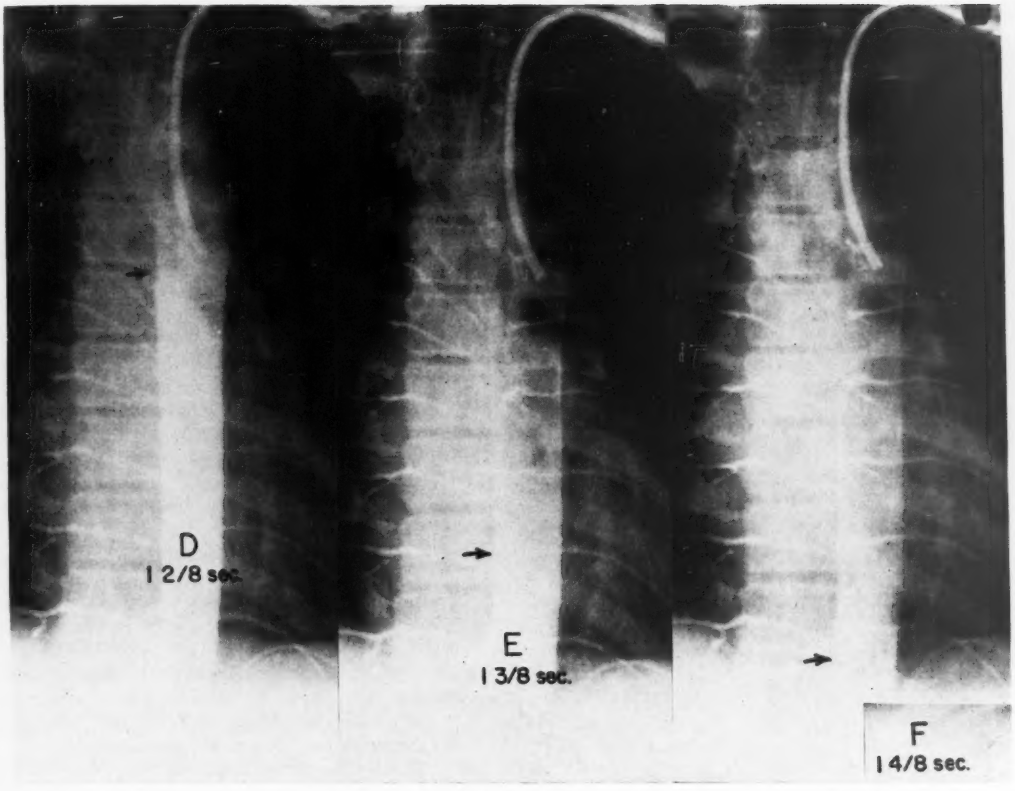


Figure 6b

Aortograms of the same patient taken after the injection of the contrast substance is completed. The "pseudocentripetal" phenomenon is no longer observed and only a forward movement of the contrast substance exists (D, E, and F).

Caution must be exercised in interpreting the movements of the opacified column of blood in the aortogram. As long as the contrast substance is still being injected, a false centripetal movement may be misdiagnosed in a normal aortogram. If the rate of blood flow is greater than the rate of injection of the contrast substance, the level of the radiopaque material moves farther distally from the site of injection during ventricular systole. With the onset of diastole, the incoming contrast substance accumulates at the area of injection, giving the false impression of a centripetal return of the opacified blood. A closer scrutiny, however, reveals that this "diastolic pseudomovement" is noted immediately at the onset of diastole, and does not show the gradual ascent of the radiopaque material characteristically seen in aortic regurgitation. The upper level of the contrast material also does not go appreciably higher than the level of the tip of the catheter. These phenomena are well demonstrated in figure 6a, which shows the serial levels of the contrast substance at systole and diastole during its injection and in figure 6b, after the injection is completed.

While this method represents another means for the physiologic evaluation of the degree of aortic regurgitation, it must be compared with other methods before its usefulness is fully established. We have not yet undertaken this comparative study. The use of both the dye-indicator technics and the present method

on the same patient would be ideal for this type of investigation.

Summary

A technic of performing retrograde aortography for the study of aortic insufficiency is presented. The aortograms demonstrate the abnormal expansile movements of the aorta, and the to-and-fro motion of the opacified vascular column in the proximal portion of the aorta with systole and diastole. These phenomena were not observed in patients without aortic insufficiency. A method for calculating the stroke volume and the volume of regurgitation from these aortograms is presented.

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A discovery is usually an unforeseen relation not confirmed in theory, for otherwise it would have been foreseen.—Claude Bernard

A Simplified Technic for the Detection of Patent Ductus Arteriosus and of Other Left-to-Right Shunts Originating from the Aorta

By EUGENE BRAUNWALD, M.D., AND WILLIAM P. CORNELL, M.D.

THE PRESENCE of an isolated patent ductus arteriosus can generally be determined by clinical examination. However, the differentiation of patent ductus arteriosus from the more unusual left-to-right shunts originating from the aorta is notoriously difficult, and in the presence of an associated intracardiac shunt the recognition of a patent ductus arteriosus may not be possible even by means of cardiac catheterization. The diagnosis of this malformation can be established by means of retrograde thoracic aortography or by indicator-dilution curves following central aortic injection.[1, 2] In this laboratory, however, these diagnostic methods have not been found to be practical as "routine" or "screening" procedures. In view of the importance of determining the presence or absence of a patent ductus arteriosus, particularly in patients for whom an open operation for an intracardiac defect is planned, efforts have been directed toward the development of a simple but accurate diagnostic technic.

The versatility, reliability, and technical simplicity of the technics utilizing injections of solution Kr^{85} for the characterization of intracardiac shunts[3–6] prompted their application to this problem. In the present study solutions of Kr^{85} were injected into the central aorta through a small radiopaque catheter inserted by way of an indwelling arterial needle and the appearance time of the isotope was detected in the expired air.

Patient Material and Methods

Twenty-two patients ranging in age from 2 to 59 years were studied. In eight of these the presence of an isolated patent ductus arteriosus was confirmed at subsequent operation. Three patients had rheumatic heart disease and there was no clinical suspicion of the presence of any circulatory shunt. In six patients an intracardiac shunt (atrial or ventricular septal defect) was present, and the absence of an associated patent ductus arteriosus was confirmed at operation. The diagnoses in the remaining patients were ventricular septal defect with aortic regurgitation, aortic stenosis and regurgitation, ruptured aneurysm of the sinus of Valsalva, aorticopulmonary window, and aorticopulmonary (Potts) anastomosis. In these patients the diagnoses were proved either at operation, at postmortem examination, or by means of retrograde thoracic aortography.

In general, central aortic catheterization was carried out by means of radiopaque poly-vinyl catheters.* These catheters are 70 cm. in length, and were sterilized in ethylene oxide gas. When the femoral artery was large enough to permit introduction of a no. 16 Cournand needle, the internal diameter of the catheter employed was .022 cm. In most instances, however, a no. 18 Cournand needle was used with a catheter of .012-cm. internal diameter. The inner surfaces of the Cournand needles were polished to facilitate passage of the catheter and their bevels rounded to prevent shearing of the catheter upon withdrawal.

Solutions of Kr^{85} in isotonic saline were prepared as outlined previously.[6] Immediately before and after each injection the patient was instructed to breathe rapidly through a mouth piece. The expired gas was led across the face of an end-window Geiger-Muller tube,† the output of which was integrated by a count-rate meter,‡ and recorded continuously on a direct-writing oscillograph. In general, less than 30 μc. of Kr^{85} was employed for each injection, and the injections were made with the tip of the catheter at various levels in the aorta.

In seven of the patients, indicator-dilution curves were also obtained in order to characterize the lesions further. Blood was always sampled from the right brachial artery. The details of the technic employed for obtaining these curves have been described elsewhere.[7]

From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

*Manufactured by Albert E. Afford, 340 Marve Avenue, Haddonfield, New Jersey.

†Type TGC 2 Geiger Tube—Tracerlab, Waltham 54, Massachusetts.

‡Model 1620B—Nuclear-Chicago, Chicago, Illinois.

Results

When the Kr^{85} was injected into the aorta near the origin of the left subclavian artery in the eight patients with a patent ductus arteriosus, its appearance in expired gas ranged from 2.5 to 4.0 seconds after injection, and the concentration rose relatively rapidly to a high peak. When the injection was made into the aorta below the level of the diaphragm, however, the appearance times ranged from 8 to 20 seconds and the concentration rose slowly to a lower peak. The differences in the appearance times between the injections made into the aorta from a point proximal and a point distal to the ductus ranged from 5.5 seconds to 16.0 seconds and averaged 9.5 seconds.

When the Kr^{85} was injected into the aorta at the level of the left subclavian artery in the eight patients without left-to-right shunts from the aorta, the appearance times in the expired gas ranged from 11 to 17 seconds, averaged 13.4 seconds, and the concentration rose relatively slowly. The appearance times were similar when the injections were made into the aorta at the level of the diaphragm and ranged from 11 to 19 seconds and averaged 14.5 seconds. In these patients the differences in the appearance times between the upper and lower aortic injections ranged from 0 to 6 seconds and averaged 1.0 second.

Illustrative Clinical Applications

Case 1

S.G., no. 02-87-58, an 8-year-old boy with known congenital heart disease, complained of increasing fatigability and dyspnea. On physical examination he was underdeveloped and presented with physical findings that suggested a ventricular septal defect with associated aortic stenosis. Right heart catheterization carried out at a university medical center revealed equal pressures in the pulmonary and brachial arteries and an oxygen "step-up" in the right ventricular outflow tract and pulmonary artery. At the National Heart Institute retrograde aortic catheterization was carried out and Kr^{85} was injected into the aorta at the level of the left subclavian artery and at the level of the diaphragm. The expired air Kr^{85} curves (fig. 1) revealed an appearance time of 3.0 seconds with a rapid rise to a high peak concentration when the injection was made into the aortic arch; the appearance time was 11.0 seconds with a gradual rise to a relatively low peak concentration when the injection was made into the aorta at the level of the diaphragm. These studies were interpreted as indicating the presence of a left-to-right shunt originating from the aorta at the level of the left subclavian artery, or proximal thereto. At operation a moderate-sized patent ductus arteriosus was closed. The aortic valve gradient measured at the operating table fell from 100 mm. Hg prior to ligation of the ductus to 50 mm. Hg following closure.

No extensive diagnostic procedures were indicated in this seriously ill patient in whom the presence of pulmonary hypertension and of a left-to-right shunt had been established previously. The Kr^{85} injections clearly indicated that a left-to-right shunt originated from the aorta. The pulmonary hypertension was thought to account for the absence of any diastolic murmur. Thus, the application of this simple diagnostic technic proved useful in developing a rational therapeutic plan for this patient.

Case 2

T.R., no. 02-79-56, a 56-year-old man was first told of a heart murmur at the age of 46 years. Nine years later he was admitted to a university hospital for an unrelated illness and a continuous murmur was noted in the upper parasternal area; right heart catheterization indicated that a moderate-sized left-to-right shunt entered the pulmonary artery. At the time of referral to the National Heart Institute, the diagnoses suggested were patent ductus arteriosus, ruptured aneurysm of an aortic sinus of Valsalva, and coronary arteriovenous fistula.

At retrograde aortic catheterization the appearance times in the expired air of $Kr,^{85}$ which had been injected into the ascending aorta and into the abdominal aorta, were identical (14 seconds), excluding the presence of a left-to-right shunt originating from the aorta (fig. 2). Indicator-dilution curves recorded oximetrically from the right ear following the injection of cardio-green dye at various levels in the descending aorta showed that a moderate degree of aortic regurgitation was present;[8] dye injected at a point 16 cm. below the origin of the left subclavian artery regurgitated to the origin of the innominate artery and was immediately detected in the right ear. Right heart catheterization revealed no evidence of any left-to-right shunt by means of the inhaled Kr^{85} test.[9]

In spite of the strong clinical suspicion that a left-to-right shunt originated from the aorta in this patient, the retrograde aortic catheterization with Kr^{85} and cardio-green injections excluded its

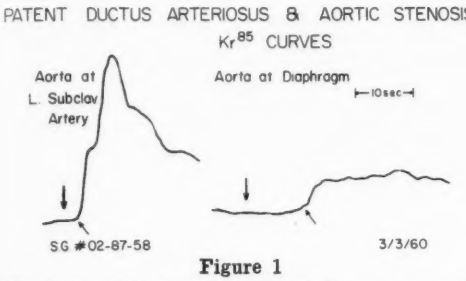

Figure 1

Expiratory Kr^{85} time-concentration curves obtained from patient S.G. The curve on the left followed injection into the aorta near the origin of the left subclavian artery, while the curve at the right followed injection into the aorta at the level of the diaphragm. The vertical arrow represents the instant of injection and the oblique arrows indicate the appearance time in the expired air. Calibration of count-rate meter was identical for both curves.

presence and indicated the existence of aortic regurgitation; the absence of any left-to-right shunt was further confirmed at right heart catheterization. This patient represents the unusual occurrence of the auscultatory finding of a "continuous" murmur resulting from an aortic valve lesion, which is presumably rheumatic in origin.

Case 3

A.G., no. 02-80-15, a 59-year-old woman, was known to have had a heart murmur all of her life. Exertional dyspnea began at the age of 40 years, and she had been in overt congestive heart failure for the 4 years preceding her admission. On physical examination the findings were typical of a patent ductus arteriosus with a large left-to-right shunt and moderately severe congestive heart failure. At retrograde aortic catheterization, Kr^{85} injections resulted in an early appearance time (4 seconds) following injection at the level of the left subclavian artery, and a delayed appearance time (20 seconds) following injection at the level of the diaphragm (fig. 3A). When cardio-green dye was injected into the aorta at the level of the diaphragm, the recirculation curve appeared 28 seconds later in the right brachial artery. In contrast, when the injection was made into the aorta at the origin of the left subclavian artery the appearance time of the dye was 13 seconds (fig. 3B); this was interpreted to indicate that the left-to-right shunt began at a point distal to the origin of the innominate artery. The earlier appearance of dye resulted from the shunting of blood through the pulmonary circulation. Had the shunt originated from the root of the aorta the appearance time of

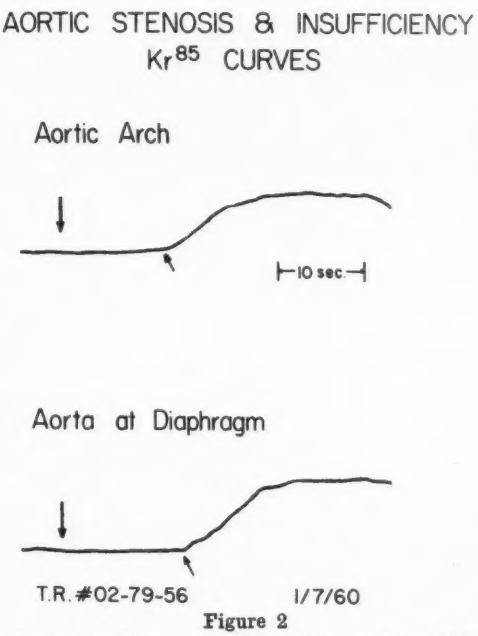

Figure 2

Expiratory Kr^{85} curves obtained from patient T.R.

dye in the right brachial artery would have been almost immediate, as was observed in patient E. S. (fig. 4).

Case 4

E.S., no. 02-83-50, a 32-year-old woman was known to have had a continuous heart murmur since birth. Six years prior to study she was thought, at another hospital, to have a patent ductus arteriosus but none was found at thoracotomy. At this time, a continuous thrill was palpated over the right ventricular outflow tract, but its origin was not clear. On examination at the National Heart Institute, the physical findings were also considered typical for patent ductus arteriosus; a grade IV/VI continuous murmur was heard best in the second intercostal space along the left sternal border, and the peripheral pulses were bounding. Retrograde aortic catheterization revealed prolonged appearance times after Kr^{85} injections into the aorta, both at the diaphragm and at the origin of the left subclavian artery. When the injection was made just above the aortic valve, however, the appearance was rapid (1 second) and the concentration rose abruptly. Indicator-dilution curves were then obtained by sampling blood from the right brachial artery (fig. 4). Injection into the aorta at the level of the diaphragm showed only the presence of recirculating dye, appearing 15.5 seconds after the injection;

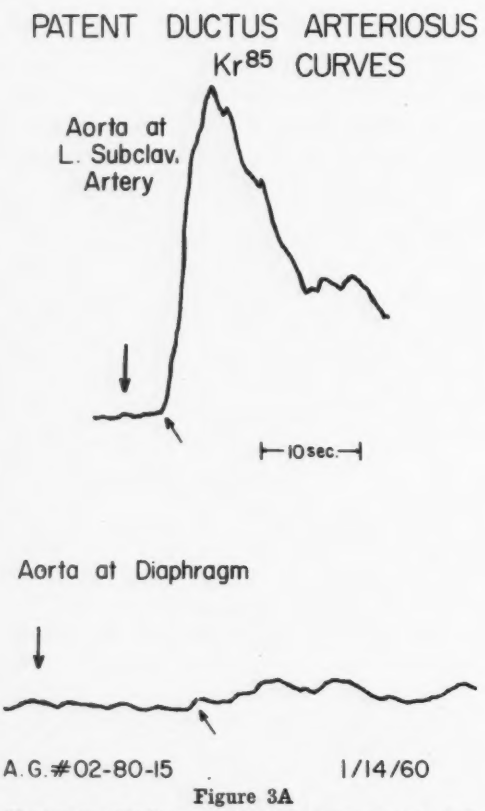

Figure 3A

Expiratory Kr^{85} curves obtained from patient A.G. The upper curve resulted from an injection proximal to the patent ductus, while the lower curve resulted from an injection below the origin of the ductus.

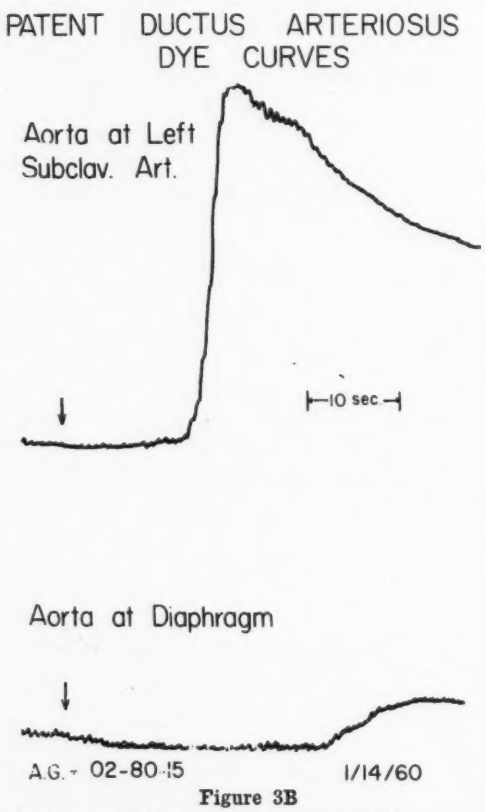

Figure 3B

Indicator-dilution curves with brachial artery sampling, obtained from patient A.G.

injection into the aorta at the origin of the left subclavian artery showed a prompt appearance (4 seconds), a rapid return to the baseline, followed by the appearance of recirculating indicator 15 seconds after injection. This curve was interpreted as showing that although some dye injected at this level regurgitated back to the origin of the innominate artery, it did not pass through the pulmonary circulation and therefore indicated that the left-to-right shunt originated at a point proximal to the origin of the innominate artery. Injection of cardio-green into the aorta just above the aortic valve resulted in a curve with three distinct peaks. The first peak occurred at 4 seconds after injection and represents that portion of the dye which passed directly into the right brachial artery. The second peak occurred 8 seconds after injection and represents that fraction of the dye which was shunted from the ascending aorta through the pulmonary vascular bed. The third peak, at 16 seconds, corresponds to the systemic recirculation curve seen in the other dilution curves.

The studies in this patient demonstrate that a left-to-right shunt originating from the aorta at the level of the left subclavian artery, i.e., a patent ductus arteriosus, can be clearly differentiated from a shunt originating from the root of the aorta. When the shunt originates from the aortic root, as in this patient, the various anatomic lesions which are responsible cannot be differentiated by either Kr^{85} or indicator-dye injections and thoracic aortography is indicated. In patient E.S., an aneurysm of the aortic sinus of Valsalva which had ruptured into the right ventricle was demonstrated by the latter technic.

Case 5

G.B., no. 03-02-65, a 6-year-old white boy was known to have had a heart murmur since the age of 3 years. He suffered from moderate limitation

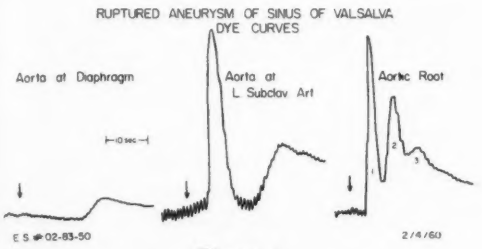

Figure 4

Indicator-dilution curves with brachial artery sampling following injection into the aorta at three different points. The three peaks in the curve resulting from aortic root injection are numbered, and described in detail in the text.

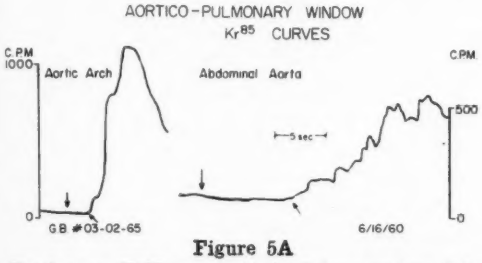

Figure 5A

Expiratory Kr^{85} curves obtained from patient G.B. The scales at either side represent the calibrations of the count-rate meter. C.P.M. refers to counts per minute.

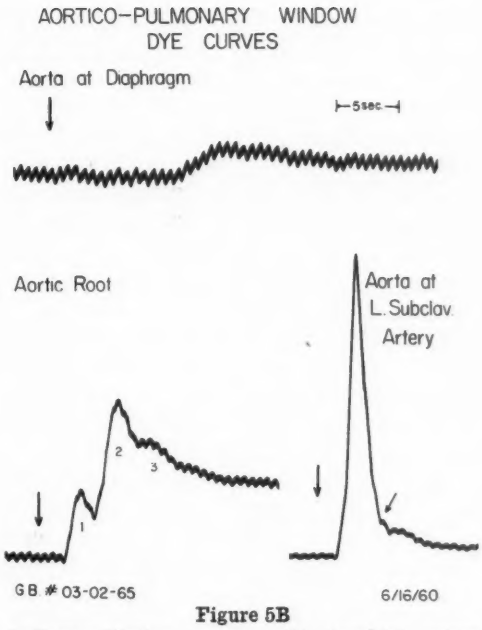

Figure 5B

Indicator-dilution curves with brachial artery sampling following injection into the aorta at three different points.

of activity and frequent respiratory infections. On examination, a grade III/VI systolic murmur was heard most prominently along the left sternal border and the second heart sound in the pulmonic area was greatly accentuated. At the time of retrograde aortic catheterization, Kr^{85} injections revealed a rapid appearance (2.5 seconds) following injection both at the aortic valve and at the level of the left subclavian artery, and an appearance time of 8 seconds following injection into the abdominal aorta (fig. 5A). In order further to localize the origin of the shunt, indicator-dilution curves were obtained from the right brachial artery (fig. 5B). Injection into the aorta at the level of the diaphragm revealed only systemic recirculation. Injection into the aorta at the origin of the left subclavian artery revealed an early peak due to dye that had regurgitated back to the origin or the innominate artery and then passed into the right brachial artery; a small interruption of the descending limb due to a small fraction of dye that had shunted through the pulmonary circulation was also present. Injection just above the aortic valve revealed, (1) a small primary curve resulting from dye passing directly into the brachial artery, (2) a larger curve resulting from the shunting of a larger fraction of dye through the pulmonary circulation, and (3) a third peak resulting from systemic recirculation (fig. 5B). The presence of a patent ductus arteriosus could be excluded, since only a very small fraction of dye injected at the level of the left subclavian artery was shunted through the lungs, while a much larger shunt was evident in the curve resulting from injection into the aortic root. The diagnosis of an aorticopulmonary window was subsequently established by means of a retrograde thoracic aortogram and was confirmed at open operation.

Discussion

The chief value of retrograde aortic catheterization with injections of solutions of Kr^{85} is in determining the presence or absence of a left-to-right shunt originating from the aorta. Perhaps the most important application of this technic will be in the study of patients with intracardiac shunts who are potential candidates for operation utilizing cardiopulmonary bypass. The presence of the intracardiac shunt may mask an associated aortico-

pulmonary shunt, since the diastolic murmur characteristic of the latter lesions is often absent in patients with pulmonary hypertension. On the other hand, patients with large, isolated intracardiac left-to-right shunts often have diastolic murmurs due to excessive blood flow across the mitral or tricuspid valve. The auscultatory findings in such patients may falsely suggest the presence of a patent ductus arteriosus, particularly when their heart rate is rapid. Because of the difficulties in determining the presence or absence of a second left-to-right shunt the data obtained at the time of right heart catheterization do not usually provide conclusive evidence regarding a shunt originating from the aorta.

When operations are carried out with the aid of cardiopulmonary bypass, the presence of an unsuspected patent ductus arteriosus, or other left-to-right shunt originating from the aorta, results in considerable technical difficulty, and occasionally a fatal outcome; large amounts of blood are pumped into the pulmonary circulation from the extracorporeal circuit and may flood the operative field before the surgeon can close the ductus or complete the repair of the intracardiac defect. Many of the open operations are performed through a median sternotomy, and ligation of a ductus arteriosus may prove difficult from this surgical approach.

The procedures described in the present report may be added to the standard right heart catheterization; their application requires only minimal additional time and does not add significantly to the risk of the procedure. If the indwelling arterial needle is inserted into the femoral artery at the beginning of the catheterization, even an additional arterial puncture can be avoided and no blood sampling is necessary. It would seem appropriate, therefore, to use the aortic Kr^{85} injections as a screening test whenever it is felt desirable to determine whether or not a left-to-right shunt originates from a point distal to the aortic valve. When the test is negative, the presence of such a shunt may be excluded with a considerable degree of reliability; the sensitivity of the injected Kr^{85} technic has been discussed in detail elsewhere,[6] and it is notable that in the series of patients described herein, the test did not fail to detect any left-to-right shunt originating from the aorta. When, on the other hand, the presence of such a shunt is indicated, other methods are usually required to determine whether it results from a patent ductus arteriosus, or any of the less common lesions at the base of the heart, i.e., aorticopulmonary window, ruptured aneurysm sinus of Valsalva, ventricular septal defect with aortic incompetence, coronary arteriovenous fistula, etc. The indicator-dilution method, utilizing right brachial artery sampling, is helpful in defining the site of origin of the shunt. When the dilution curves show that the shunt originates from the aorta near the origin of the left subclavian artery (fig. 3B) the diagnosis of a patent ductus arteriosus is established. However, when the shunt originates proximal to this point (figs. 4 and 5B) thoracic aortography is usually necessary in order to define the specific malformation responsible.

Summary

A simplified technic for the detection of left-to-right shunts originating from the aorta is described. A thin, radiopaque catheter is introduced into the aortic arch through a Cournand needle placed in the femoral artery, and injections of a solution of Kr^{85} are made. In the presence of a shunt the injected Kr^{85} is rapidly detected in the expired air but in the absence of a shunt the appearance time of Kr^{85} in the expired air is delayed. When an aortic shunt is present it may be localized by means of injections of cardiogreen dye at various points in the aorta by sampling the blood from the right brachial artery. The value of these technics is illustrated by descriptions of their application in five patients with various forms of congenital or acquired heart disease.

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Aneurism of the Aorta; Singular Pulsation of the Arteries, Necessity of the Employment of the Stethoscope

BY DOMINIC JOHN CORRIGAN, M.D.

Lecturer on the Institutes and Practice of Medicine; one of the Physicians of the Sick-Poor Institution, Dublin.

Mr. J. D.——e, a builder, (Cole's Lane), called on me, for the first time, in the early part of June. His complaint commenced about four months before that period, with sense of oppression and straitness in his chest, succeeded by cough, occasionally convulsive; the cough and oppression of chest always relieved by mucous expectoration. He might, at that time, have been selected as a man presenting the very vigour of health, finely made, full in flesh, of a florid complexion, and active in his limbs. . . .

On stripping him, the first remarkable appearance that caught the eye, was a singular pulsation of all the arterial trunks of the upper part of the body. As his arms hung by his side, the whole tract of the branchial and carotid arteries was thrown out in strong relief, at each impulse of the heart, as if the vessels, from having been previously comparatively empty, had become suddenly filled.—*The Lancet* 1:586, 1829.

SPECIAL ARTICLE

William Harvey and His Contributions

By FREDERICK G. KILGOUR

Life and Times

THE HARVEIAN Orator of 1662, probably Sir Charles Scarburgh but perhaps someone else who knew Harvey well, proclaimed that Harvey "thought again and again and for a long time how he could raise himself effectively from the ground and place his head among the stars and at last there settled in his mind the wish to embrace medicine."[1] Harvey certainly succeeded in rising to a place amongst the stars, and the "ground," so to speak, from which he raised himself was Folkestone, on the strait of Dover, in Kent. Here, William Harvey was born on April 1, 1578, twenty years after the first Elizabeth had ascended the throne of England. William was the eldest son in a family of seven sons and two daughters. His father, Thomas Harvey, was a Turkey merchant as, subsequently, were five of Harvey's brothers.

Harvey was born into a world in ferment—intellectual, religious, social, economic, and political. Indeed, the year 1588, when young Harvey went off to King's School, Canterbury, was the year when the *Invincible Armada* of 132 vessels and over 3,000 cannon attempted its ill-fated invasion of England; Drake struck his most damaging blows in an attack that began off Calais, across the Strait from Folkestone.

Harvey attended King's School, Canterbury for five years. It was probably during this period that "there settled in his mind the wish to embrace medicine," for Sir Thomas Barlow[2] has pointed out that the scholarship that enabled him to enter Caius College, Cambridge, in May 1593, was essentially a medical scholarship. Although he received his Arts degree in 1597, Harvey stayed on at Cambridge until Christmas, 1599, when his scholarship lapsed, but during his last three years, he was absent for various periods totaling sixteen months, presumably because of illness.[3] Details of Harvey's activities at Cambridge are lacking, but since he retained his scholarship for six years, he probably fulfilled its conditions, among which were that he should first study subjects related to medicine and then subjects within medicine. The author of the recently discovered Harveian Oration in speaking of Harvey's Cambridge days said, "He devoted himself assiduously to his studies and turned with greatest zeal to philosophy. After the manner of the ancient philosophers (as they say about Plato and Pythagoras) he thought that he should travel as widely as possible in the hope of acquiring thereby some of their teaching and wisdom. Therefore this genius, who was to become a second Aesculapius, did not continue to remain in this country."[4]

In 1600, the last year of the century of renaissance and reformation, Harvey proceeded to Padua to study medicine. He could not have chosen a better school, for the renowned north Italian University was the foremost scientific school of the sixteenth century. In Harvey's time, Galileo was its greatest genius. It was with the celebrated anatomist, Fabricius ab Aquapendente, however, that Harvey studied. Fabricius instructed him in the logic and technics of experiment and introduced him to the valves in the veins and

From the Yale Medical Library, Yale University School of Medicine, New Haven, Conn.

in chick embryology—subjects that were destined to be of great importance in the two fields of his subsequent publications. Various Harveian biographers have interpreted the exuberant language of Harvey's 1602 Paduan diploma to be a testimonial to his brilliance as a student. But J. F. Payne commented, "Unfortunately it is nothing of the kind. This grandiloquent language was a common form, and occurs in several Paduan diplomas which I have seen. Every doctor was said to have answered 'marvellously,' and far surpassed the high expectations which had been entertained regarding him. Harvey's diploma was neither more nor less than the usual one."[5]

Harvey returned to England later in 1602 to be incorporated as Doctor of Medicine at Cambridge and to enter upon the practice of medicine in London. The England to which Harvey returned was a dynamic country. During the previous century English politics, economic well-being, and culture had been steadily changing. Under Elizabeth I, English nationalism welded the British into a single group. English ships had begun to sail the seas. England was rapidly becoming a world power in politics, in economics, in the arts and sciences. Two great movements from continental Europe had contributed their influences to the British—the Reformation from Germany and the Renaissance from Italy. In 1531 Henry VIII had renounced the Pope for political and personal reasons. During the century, the Reformation made this split permanent, and it was a Protestant England to which Harvey returned in 1602. From Italy, the Renaissance had stimulated artistic activity, particularly in literature. It was the age of Marlowe, Shakespeare, Ben Jonson, and Beaumont and Fletcher.

But most important of all there came from Italy a scientific attitude of mind, which was wholly new to the world. More than any other one factor, the experimental attitude was liberating Western Christendom from scholasticism. During the seventeenth century, this liberation was completed, and Newton produced the first great triumph of modern science. It is experimental science that differentiates western civilization from the rest of the world, and Harvey played an important role in the early progress and spreading of the new science. His contemporaries were Galileo, Kepler, Bacon, Gilbert, Stevin, Napier, Descartes, and a host of lesser men. Their successors completed the intellectual revolution that brought experimental science into being.

Whether or not Harvey had any notion of the circulation of the blood when he left Padua, is not known. In any event, he proceeded to practice medicine in London and the Royal College of Physicians elected him as candidate in 1604, also the year of his marriage. Three years later the College elected him a Fellow. St. Bartholomew's Hospital appointed him Physician of the Hospital in 1609. The College of Physicians honored him in 1615 by appointing him Lumleian Lecturer. The appointment was for life, and Harvey was to give a series of anatomic and surgical lectures over a period of six years. Having completed the first series, he would then start on the second six-year cycle. His lecture notes for the 1616 series are still in existence and contain the earliest record of Harvey's work on the circulation of the blood. Harvey gave these lectures in the week preceding Shakespeare's death. During the next decade, Harvey continued to rise socially and professionally. James I, who had succeeded Elizabeth the year after Harvey returned from Padua, appointed him Physician Extraordinary to the King in 1618, and Francis Bacon was one of his patients. Harvey was not sympathetic to Bacon's views on science, for John Aubrey records that Harvey admired Bacon's "wit and style, but would not allow him to be a great Philosopher. Said he to me, *He writes Philosophy like a Lord Chancellor,* speaking in derision; *I have cured him.*"[6]

John Aubrey's "brief biography" is the most extensive record extant of Harvey that was written by one who knew him. Aubrey did not become acquainted with Harvey until 1651, however, and did not set down his recollections until more than two decades after Harvey's death. Those writing about Harvey, as well as others, usually label Aubrey as

"unreliable," but his most recent editor, Oliver Lawson Dick, says, "he was sometimes inaccurate, it is true but he was never untruthful, and the distinction is a most important one."[7] Aubrey's life of Harvey has its inaccuracies, but it contains more information about Harvey as a person than any other source.[8] He was accurate when he wrote, "Ah! my old Friend Dr. Harvey—I knew him right well." Describing Harvey, Aubrey says, "He was not tall; but of the lowest stature, round faced, olivaster complexion; little Eie, round, very black, full of spirit, his haire was black as a Raven, but quite white 20 years before he dyed." "He was very Cholerique; and in his young days wore a dagger (as the fashion then was) but this Dr. would be to apt to draw out his dagger upon every slight occasion." Sir Geoffrey Keynes thought that this description agreed well with the Harvey portrayed in his important discovery, a Harvey portrait of about 1622.[9]

Late in 1627 Harvey became one of the eight Electors of the Royal College of Physicians. It was in the next year, 1628, when he was fifty years of age, that his greatest work appeared—the "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus." From 1628 to 1642 Harvey was a busy man writing, experimenting, traveling in Europe, performing his duties at St. Bartholomew's Hospital, to say nothing of tending to his own practice about which Aubrey had heard him say, "that after his Booke of the *Circulation of the Blood* came out, that he fell mightily in this Pracitize, and that t'was believed by the vulgar that he was crack-brained."

Charles I, who had succeeded James I in 1625, appointed him Physician in Ordinary in 1631, and his loyalty was to cause him great anguish and to cast a shadow over the last fifteen years of his life. When the Civil War began in 1642, Harvey sided with his King and spent most of the next four years in Oxford, the royal headquarters. At the start of the War his house in London was plundered, his goods and papers being destroyed, and "he often sayd, That of all the losses he sustained, no grief was so crucifying to him as the losse of these papers, which for love or money he could never retrieve or obtaine."[10]

After the fall of Oxford in July 1646, Harvey returned to London and resumed the practice of medicine. Although he was in his sixty-ninth year and afflicted with gout, he was quite active despite his being a royalist. He expressed his position when Dr. George Ent called on him at Christmas time 1650 and "asked if all were well with him? 'How can it,' said he, 'whilst the Commonwealth is full of distractions, and I myself am still in the open sea. And truly,' he continued, 'did I not find solace in my studies, and a balm for my spirit in the memory of my observations of former years, I should feel little desire for longer life.'"[11] The solace in his studies consisted of, among other activities, writing his "Exercitatio Anatomica de Circulatione Sanguinis," published at Cambridge and Rotterdam in 1649 and probably in writing his "Exercitationes de Generatione Animalium" first published at London in 1651 and followed by three other editions printed in Holland the same year. Moreover, he may have written other treatises referred to in the "De Generatione" but never published.

During this period he was living in his brothers' houses in London and in the country such as his brother Eliab's at Roehampton where, according to a great-niece, "he used to walk out in a morning, combing his hair in the fields." He was requested to be President of the Royal College of Physicians in 1654 but declined because of advanced age and ill health. Three years later, on the third of June, 1657, he died, following a failure of that circulatory system which he had been the first to propose nearly thirty years earlier. John Aubrey, who "was at his Funerall, and helpt to carry him into the Vault," described the end: "the morning of his death about 10 a clock, he went to speake, and found he had the dead palsey in his Tongue; then he saw what was to become of him, he knew there was then no hopes for his recovery, so presently sends for his brother and young nephewes to come-up to him, to whom he gives one

his Watch ('twas a minute watch with which he made his experiments), to another another thing, etc., as remembrances of him; made a signe to Sambrooke, his Apothecary, to lett him blood in the Tongue, which did little or no good; and so ended his dayes. The Palsey did give him an easy Passe-port."

Harvey's Writings

Harvey published three major works of which the first, the "De Motu Cordis" of 1628, is, of course, the most important. The second, the "De Circulatione Sanguinis" (1649) consisting of two letters to Jean Riolan, is for all practical purposes a supplement to the "De Motu Cordis." The third, "De Generatione Animalium," appeared in four separate editions in 1651 as already noted. Sir Geoffrey Keynes' admirable "Bibliography"[12] thoroughly describes the various editions of these works giving the locations of copies as well as the editions of "Opera Omnia" and several "Miscellanea." In all, Keynes lists some fifty-five different editions and translations of the first three titles of which forty-one are of the "De Motu Cordis" —evidence in itself of greatness.

Harvey's published writings are, however, but a segment of his total literary output, for there is reason to believe that perhaps as many as eighteen further treatises existed in manuscript in the seventeenth century.[13] Today only two are known to be extant; both are volumes of notes, and both are in the British Museum. One, "Prelectiones Anatomiae Universalis" which is his Lumleian lecture notes of 1616, was published in 1886, but the other on muscle anatomy and the local motion of animals remained unpublished until the second part of it appeared in 1959.[14]

Harvey as a Physician

Speaking of Harvey as a physician, the 1662 Harveian Orator declared, "He practised this art with such skill that it seemed as though he had not acquired the knowledge but had rather been born with it."[15] Aubrey, on what at first glance might appear to be the other hand, reported, "All his Profession would allow him to be an exellent Anatomist, but I never heard of any that admired his Therapeutique way. I knew severall practisers in London that would not have given 3d. for one of his Bills; and that a man could hardly tell by one of his Bills what he did aime at."[16]

There is probably a good bit of truth in both the statements. Obviously Aubrey is referring to "cook-book" practitioners who bought up the prescriptions of others as though they were so many recipes. However, from the evidence available it would appear that Harvey practiced rational medicine, and his prescriptions would naturally have little appeal for recipe collectors.

Harvey did not introduce any important new therapeutic procedures, but he does seem to have been an able physician. Perhaps the best way to give a brief picture of him as a clinician is to cite one of his cases.

"The wife of a doctor of divinity was brought to me; a lady of a very tolerable constitution, but who was barren and having an extreme desire for progeny, had tried all kinds of prescriptions in vain. In her the catamenia appeared at their proper period; but at times, especially after horse exercise, a bloody and purulent discharge came from the uterus, and then, in a short time, ceased suddenly. Some considered the case as one of leucorrhoea; others, led chiefly by the fact that the discharge was not continually present, and in small quantities, but appeared by intervals and in abundance, suspected a fistulous ulcer; whereupon they examined the whole vagina by means of a speculum uteri, and applied various remedies, but in vain; when I was at length called to her. I opened the uterine orifice, and immediately two spoonfuls of pus came away of a sanious character and tinged with streaks of blood. On seeing this I said that there was a hidden ulcer in the uterine cavity, and by applying suitable remedies I restored her to her former state of health. But during the time when I was engaged in her cure, when the ordinary remedies did not appear to be doing much good, I applied stronger ones, suspecting as I did that the ulcer was of long standing, and perhaps covered by exuberant granulations. I

therefore added a little Roman vitriol to the injection employed previously, the effect of which was to make the uterus contract suddenly and become as hard as a stone; at the same time various hysterical symptoms showed themselves, such, I mean, as are generally supposed by physicians to arise from constriction of the uterus, and the rising of 'foul vapours' therefrom. The symptoms continued some time, until by the application of soothing and anodyne remedies the uterus relaxed its orifice; upon which the acrid injection, together with a putrid sanies, was expelled, and in a short time the patient recovered."[17] Despite the fact that a modern gynecologist would not sanction the injection of so powerful an astringent as cupric sulfate into the uterus, the rationale of Harvey's treatment of this case is clear. Incidentally, Harvey says, "I have introduced this account from my 'medical observations' "—one of his missing manuscripts.

Harvey's ability as a practitioner was enhanced by his knowledge of pathology the value of which in application he thoroughly understood. He stated the purpose of his intention to print his "Medical Anatomy; or Anatomy in its Application to Medicine" (alas, also among his missing manuscripts) was that he might "relate from the many dissections I have made of bodies of persons diseased, worn out by serious and strange affections, how and in what way the internal organs were changed in their situation, size structure, figure, consistency, and other sensible qualities, from their natural forms and appearances, such as they are usually described by anatomists . . . and from pathology the use and art of healing, as well as occasions for the discovery of many new remedies, are perceived."[18]

If Harvey's missing "Medical Observations" and "Medical Anatomy" were available, it would be possible to render a more complete evaluation of Harvey as a clinician. But the missing treatise which would be most exciting to have for this purpose was one supposed to be entitled "A Practice of Physick Conformable to his Thesis of the Circulation of the Bloud." But without these documents one can concur with Sir Thomas Barlow that Harvey was "an experienced pathologist, a learned physician, and that he had the qualifications of a good all-round practitioner."[19]

Harvey's Contributions to Embryology

The "De Generatione Animalium" is the largest of Harvey's published writings. In Robert Willis' one-volume English translation, "The Works of William Harvey, M.D.,"[20] it occupies 444 pages while the "De Motu Cordis" has 86 pages and the "De Circulatione Sanguinis" but 55. The first three quarters of the book contain a discussion of chick embryology followed by a section on reproduction in the deer. It concludes with three relatively brief sections entitled "On Parturition," "Of the Uterine Membranes and Humours," and "On Conception."

The great and lasting interest in the "De Motu Cordis" has led to a neglect of the "De Generatione Animalium" which, it must be acknowledged, has its short-comings. In the 1930's, two qualified authorities, Joseph Needham and Arthur William Meyer, analyzed the book extensively, and their findings have not been superceded to any important extent. Meyer, whose investigation was particularly extensive and valuable, catalogues "such erroneous conclusions as that fertilization is due to an influence like that of the stars; that development begins even in unfertilized eggs; that an egg grows before the vital principle enters it; that nothing exists in the uterus of the deer until six weeks after mating; that the uterus generates the "ovum" of mammals; that nothing of the semen enters the mammalian uterus; that the mammalian fetus delivers itself, and that if it were expelled by the uterus it would present the feet instead of the head foremost; that the unborn infant sucks in utero, and that if it did not do so, it would not know how to nurse after it is born; that the human fetus swallows amniotic fluid for food and that its birth is due to hunger; that the fetal intestines contain excrementitious material identical with that formed from the ingestion of milk; that the

sexual products are not formed in the testes and ovary as commonly held in his time; that there is no placenta in the hog or horse: and so forth.''[21] Meyer's book is far from being negative in its conclusions as this quotation might indicate; it was chosen as an excellent succinct statement of Harvey's errors.

On the other hand, the following quotation from Needham is an equally excellent and succinct summary of Harvey's contributions to embryology.

''1. There can be no doubt that the doctrine *omne vivum ex ovo* was an advance on all preceding thought. Harvey's scepticism about spontaneous generation antedated by nearly a century the experiments of Redi. It is important to note that he was led to his idea of the mammalian ovum by observations on small embryos surrounded by their chorion and no bigger than eggs, for the follicle was not discovered until the time of Stensen and de Graaf, and the true ovum not till the time of von Baer.

2. He identified definitely and finally the cicatricula on the yolk membrane as the spot from which the embryo originated.

3. He denied the possibility of generation from excrement and from mud, saying that even vermiparous animals had eggs.

4. He discussed the question of metamorphosis (preformation) and epigenesis, and decided plainly for the latter, at any rate for the sanguineous animals.

In addition to these achievements, there are others, perhaps less noticed hitherto, but equally important.

5. He destroyed once and for all the Aristotelian (semen-blood) and Epicurean (semen-semen) theories of early embryogeny. This was perhaps the biggest crack he made in the peripatetic teaching on development, but, in spite of it, Sennertus, van Linde and Sylvius adhered to the ancient views, and Cyprianus, in 1700, had the distinction of being the last to support them in a scientific discussion, though Sterne in *Tristram Shandy,* as late as 1759, referred to them in a way that shows they still lived on in popular thought.

6. He handled the question of growth and differentiation better than any before, anticipating the ideas of the present century.

7. He settled for good the controversy which had lasted for 2,200 years as to which part of the egg was nutritive and which was formative, by demonstrating the unreality of the distinction.

8. He set his predecessors right on a very large number of detailed points, such as the nature of the placenta.

9. He made a great step forward in his theory of foetal respiration, though here he did not consolidate the gain.

10. He affirmed that embryonic organs were active, and that the embryo did not depend on external aid for its principal physiological functions.''[22]

These statements of Meyer and Needham taken together form the best brief evaluation of Harvey as an embryologist that is available.

Harvey's Contributions to Cardiovascular Physiology

William Harvey was a life-long investigator of the cardiovascular system. His lecture notes of 1616 have a sufficient number of new observations on the heart and blood vessels to make it certain that he had been investigating them for some years. His great work, the ''De Motu Cordis'' of 1628, contains many more new findings, including his celebrated quantitative work. The ''De Circulatione Sanguinis'' of 1649 is essentially a supplement to the ''De Motu Cordis'' and has still further results that he had accumulated in the two decades following the publication of his masterpiece. An example of his continuing work is his repeated efforts to perform Galen's experiment of inserting a reed or tube into an artery and then tying a ligature about the artery over the tube. Galen had found that there was a pulse in the artery before he tightened the ligature but not afterwards. He concluded that the pulse was not the function of the blood within the artery but of the arterial wall. Something had gone wrong during Galen's experiment; perhaps blood clots formed in the tube. In Harvey's 1616 lecture notes he wrote ''Galeni experimentum de

fistula Impossible," and twelve years later in the Introduction to the "De Motu Cordis," he said, "I have neither made this experiment of Galen's, nor do I believe it can be done easily in the living body because of the excessive loss of blood from the artery." However, in the "De Circulatione Sanguinis," he recorded that he had succeeded in doing Galen's experiment and found that there was a pulse beyond the tube after the ligature had been drawn up. But he did not cease investigations in 1649. Just before his seventy-third year in 1651, he wrote to P. M. Slegel of Hamburg telling of a new demonstration of the pulmonary transit[23]—in fact the only experimental demonstration of the pulmonary transit that Harvey contrived. He was truly a lifelong worker.

As has been mentioned, Harvey's Lumleian lecture notes of 1616 contain the earliest record of his work on the circulation. Sheets seventy-two through eighty of this ninety-eight sheet volume contain notes on the cardiovascular system with particular emphasis on the heart. It is perfectly clear from these notes that Harvey was lecturing on the circulation of the blood in 1616. He had already done much of the experimental work that he included in the "De Motu Cordis," some sections of which follow closely the outline of his notes. The last page reads in translation, "It is proved by the structure of the heart that the blood is continuously transferred through the lungs into the aorta, as by two clacks of a water bellows to raise water. It is proved by the ligature that there is a passage of blood from the arteries to the veins. It is therefore demonstrated that the continuous movement of the blood in a circle is brought about by the beat of the heart. Is this for the sake of nutrition, or the better preservation of the blood and members by the infusion of heat, the blood in turn being cooled by heating the members and heated by the heart?"

What caused Harvey to think of the possibilty of the circulation of the blood, and when did it first occur to him? The second question cannot be answered with accuracy, but fortunately Robert Boyle asked Harvey the first question the only time he met him not long before Harvey's death. Harvey answered, "that when he took notice that the Valves in the Veins of so many several Parts of the Body, were so Plac'd that they gave free passage to the Blood Towards the Heart, but oppos'd the passage of the Venal Blood the Contrary way: He was invited to imagine that so Provident a Cause as Nature had not so Plac'd so many Valves without design that no Design seem'd more probable than that, since the Blood could not well, because of the interposing Valves, be sent by the Veins to the Limbs; it should be sent through the Arteries, and Return through the Veins, whose Valves did not oppose its course that way."[24]

Harvey most certainly learned of the valves in the veins from Fabricius with whom he studied at Padua so that it is possible—indeed probable—that Harvey first conceived his idea of the circulation before he left Padua in 1602.

However, Harvey did not publish his renowned concept of the circulation, his greatest contribution to medical science, until 1628 in his "De Motu Cordis." The finished book printed in Latin at Frankfurt, Germany, has seventy-two pages. It appears from a reading of the "De Motu Cordis" that the entire book was not written at one time as Chauncey Leake has pointed out,[25] for the style and spirit of some chapters are entirely different from other chapters. The introduction in which Harvey describes and ridicules the current theories of the cardiovascular system has a very vigorous and emotional style including a few expletives; it is quite unlike the rest of the book. Chapter IX entitled, "The Circulation of the Blood is Proved by a Prime Consideration" concludes with a reference to the anastomosis of veins and arteries and the statement that Harvey would now inquire into the subject. Chapter X called "The First Proposition Concerning the Amount of Blood Passing from Veins to Arteries, During the Circulation of the Blood, is Freed from Objections and Confirmed by Experiments"

contains nothing on anastomosis. However, Chapter XI, "The Second Proposition is Proven," constitutes a discussion of anastomosis. It is obvious that Harvey inserted Chapter X between Chapters IX and XI after he had originally written the latter two as successive chapters.

The book can be conveniently thought of as consisting of five sections: (1) introductory, (2) movement and function of the heart, (3) pulmonary transit, (4) systemic transit, and (5) supplementary arguments. Harvey included two dedications in the "De Motu Cordis;" one is to King Charles and the other "To His Very Dear Friend Doctor Argent the excellent and accomplished President of the London College of Physicians, and to other learned Physicians, his esteemed Colleagues." Dr. Argent was President of the College from 1625 to 1627. Therefore, Harvey probably finished the book for publication in 1627 and wrote the main body of the book during the previous year or more. In addition to the two dedications and the introduction, the "De Motu Cordis" has seventeen short chapters. First his friends had requested him to make known his discovery so that everyone could learn of it and next, he published it as a defense against ridicule. He also thought that he should publish the "De Motu Cordis" because Fabricius, his old professor, had written on nearly all parts of animals except the heart. And last he thought that by publishing his discovery he would open the path for others to make further progress. He was certainly correct in this opinion.

Chapters II through V are a remarkable analysis of the movement of the heart, arteries, and atria, and an equally remarkable analysis of the function of the heart. Harvey gives the first clear statement of the apex beat, of the muscular character of the heart, and of the origin and conduction of the heart beat. He also demonstrates that the pulse in the arteries is due to the impact of the blood ejected from the heart into the arteries as when "one blows into a glove," a phrase which he also used in his 1616 lectures. The current interpretation of the pulse following Galen was that it was a wave along the arteries originating from the motion of the heart; it was a phenomenon of the arteries and not of the pressure of the blood within the arteries. He correctly concludes in Chapter V that "the principal function of the heart is the transmission and pumping of the blood through the arteries to the extremities of the body."

Chapters VI and VII describe the pulmonary transit, the route that the blood follows in its passage from the veins to the arteries. Although Realdo Colombo had argued for the pulmonary transit seventy years earlier, some anatomists in 1628 still did not accept Colombo's thesis. Referring to Colombo, Harvey cites his observations and strengthens them with comparative anatomic demonstrations from lungless animals and embryology. These two chapters are the weakest part of the book, and it was not until 1651, as already noted, that Harvey devised an experimental demonstration of the pulmonary transit using a heart-lung preparation; Jan de Wale had contrived an experiment in a living animal a decade earlier.[26]

Chapters VIII through XIV demonstrate the total circulation. Harvey employs three "Propositions" for his arguments: first, the amount of blood in the body must pass through the heart in a short time and that the amount of blood passing through the heart could not be supplied by the food consumed as would be the case according to the Galenic concept; second, the amount of blood going to the extremities is much greater than needed for the nutrition of the body; and third, the blood continuously returns to the heart from the extremities through the veins.

The first proposition is Harvey's famous quantitative work, the amount of blood ejected by the heart. To make his calculation Harvey had to measure the pulse rate and the amount of blood that the heart ejects with each beat. Here, he tackled a tough problem; even today there is no widely accepted figure for cardiac output. The determination of cardiac output is most difficult, and the various procedures for measuring it give results that vary as much as 25 per cent. The lowest figure, how-

ever—one dram, apothecaries weight—which Harvey used was only one-eighteenth of the lowest calculation accepted today. How could Harvey have made such a ridiculously incorrect measurement and at the same time use it to demonstrate such an important discovery?

It is a fairly simple matter to measure the pulse, but even here Harvey was inaccurate. He often uses a pulse rate of thirty-three per minute, about half the average rate in humans. Aubrey was quoted as reporting that Harvey while dying gave one of his nephews his minute watch which he had used in his experiments. If he did use a minute watch to time the pulse, he certainly must have obtained a figure higher than thirty-three per minute. And so he did, for in one calculation he reported that in some individuals the pulse is sixty-seven, one hundred, and one hundred thirty-three.

By using a pulse rate of thirty-three and one dram for the weight of blood ejected at each beat as the lowest estimates in his calculations, Harvey obtained a result, when he considered two or more beats, that was one thirty-sixth the lowest accepted value today. The difficulties of measuring cardiac output have been mentioned, but one cannot explain Harvey's use of a thirty-three per minute pulse rate on the basis that it is a difficult measurement to make. The question, "How could Harvey have made such an important discovery by using such inaccurate measurements?" still remains to be answered.

The answer is that Harvey showed that the total weight of blood ejected over half an hour far exceeded the weight that would be sup plied by food and indeed exceeded the total weight of blood in the body. His third calculation including man reads, "And so it may be inferred, that if at one beat the heart in man, the sheep, or the ox ejects but one dram of blood, and there are 1,000 beats in half an hour, in this interval there will have been 10 pounds 5 ounces [3,888 grams] expelled; if 2 drams at a single beat, then 20 pounds 10 ounces [7,776 grams]; if half an ounce, then 41 pounds 8 ounces [15,552 grams]; and if one ounce, the total would be 83 pounds and 4 ounces [31,104 grams] all of which would be transferred from the veins to the arteries [by the heart] in half an hour." This calculation was a blow to the Galenic concept; it was obvious that the ingested food could not produce blood in these amounts. In his other calculation involving man, Harvey states, "In half an hour the heart will make more than 1,000 beats, in some as many as two, three, and even four thousand. Multiplying the number of drams ejected by the number of beats there will be in half an hour either 3,000 drams, 2,000 drams, 500 ounces or some other proportionate quantity of blood transferred into the arteries by the heart, but always a larger quantity than is contained in the whole body." In this calculation the lowest weight, 2,000 drams, is equal to 7,776 grams, which is little above the blood volume of average man. The reason that Harvey could make such great errors in his measurement of pulse and stroke volume of the heart was that he employed the cumulative weight of blood ejected by the heart and the figure kept getting larger and larger. Using his lowest estimates, Harvey could have shown that in ten hours the heart would eject an amount of blood weighing more than the average man.[27]

Harvey's demonstration of his second proposition, the amount of blood going to the extremities is much greater than needed for the nutrition of the body, is not as impressive because he does not use any specific weights. His arguments are largely inference. In the course of the discussion, however, he makes the important point that the blood must pass from the arteries to the veins in the extremities. By using the type of bandage around the upper arm that was used in letting blood, he showed that the veins would swell with blood but not the arteries. When he put the bandage on so tightly that the pulse in the artery stopped, the veins would not swell. From these observations he reasoned correctly that the blood entered the extremities through the arteries and passed to the veins.

It only remained for him to show that the flow of blood in the veins was toward the heart and not away from it as the Galenic

concept held. This he did by using the bandage around the upper arm that stopped the flow in the veins but allowed the pulse in the artery to continue. The veins, of course, would swell. Fabricius had pointed out that the little bumps in the swollen veins were the valves. Harvey showed that by pressing one's finger along a vein from below one valve to above the next valve and thereby forcing the blood up the vein that the blood did not return to the emptied section of the vein. This experiment is the only one illustrated in Harvey's book, and the illustrations are based on those in Fabricius' "De Venarum Ostiolis."

The last three chapters of the book contain philosophical and observational arguments supporting the circulation of the blood but which by themselves do not demonstrate it. For instance, he points out that the rapid spread of infections throughout the body is accomplished by the circulation. The Galenic concept of the flow of the blood could not explain this phenomenon.

Harvey's second publication, the "De Circulatione Sanguinis" of 1649, consists of two letters or "disquisitions" addressed to Jean Riolan, Professor of Anatomy at Paris, and is essentially a supplement to the "De Motu Cordis" which Riolan had criticized. The new experimental observations in the "De Circulatione Sanguinis" are important but do not have the great significance of Harvey's earlier work. The only quantitation in the "De Circulatione Sanguinis" is the measurement of equal volumes of blood in two cups.

What are the principal features of Harvey's discovery? The essential factors of the cardiovascular system that effect the circulation of the blood are, of course, the heart pumping the blood, the passage of the blood through the lungs and its return to the heart, and the similar passage through the extremities. When Harvey began his work, he already knew of the pulmonary transit. His contributions were an improved anatomic description of the heart and the discovery that the heart pumps the blood into the arteries. As for the vascular system, he showed that blood, pumped by the left heart, flowed out through the arteries to the extremities and returned through the veins to the right heart. Before Harvey, anatomists thought of the pulmonary transit as a route whereby the blood flowed from the veins to the arteries; it is not by itself a "circulation." Harvey, however, clearly established the total circulation of which the pulmonary transit is but one part. Harvey did not contribute any important anatomic discoveries of the vascular system. Indeed, he was unable to demonstrate the capillaries although he certainly tried to do so. It remained for Marcello Malpighi, born the year the "De Motu Cordis" was published, to make this important discovery. As for an explanation of the function of the circulation, Harvey was at a loss as the questions from his Lumleian lecture notes indicate, and it is doubtful that a useful interpretation could have been developed in Harvey's time. "Yet," as John C. Curtis described the situation, "the phenomena of the very circulation used were so striking as to cry aloud for elucidation; for Harvey's own clinching statement that the heart drives into the aorta at least one thousand drachms of blood in half an hour, the *reductio ad absurdum,* which cut the ground from under the feet of his opponents, left him helpless in his turn to account for the need of so huge a flooding of the arteries."[28]

It is important, however, not to think of Harvey's contribution solely in terms of discovery and description of anatomic structure and physiologic function. His greatest contribution was the development of the concept of the circulation that has been a most fruitful idea and still suggests new avenues of investigation—the real test of any concept.

Some three weeks after Harvey entered his eightieth year and a little more than a month before he died, he wrote a letter to John Vlackfeld, Physician at Harlem, which read in part, "But it is in vain that you apply the spur to me, at my present age, not mature but declining, to gird myself for any new investigation. For I now consider myself entitled to my discharge from duty. It will, however, always be a pleasant sight for

me to see distinguished men like yourself engaged in this honorable arena.''[29] How pleased he would be if he could look in on the arenas of today!

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In the meantime this I know and declare to all men, that sometimes the blood passes in less, sometimes in more abundant quantitie, and the circuit of the blood is perform'd sometimes sooner, sometimes slower, according to the age, temperature, external and internal cause, accidents natural or innatural, sleep, rest, food, exercise, passions of the mind, and the like.—William Harvey. *De Motu Cordis,* 1628.

CLINICAL PROGRESS

The Clinical Value of Vectorcardiography

By FRANKLIN D. JOHNSTON, M.D.

SOME WORKERS, with great enthusiasm about the clinical value of vectorcardiograms, may, after reading this article, believe it should be classified under some heading other than *Clinical Progress,* but the writer hopes that the discussion will at least point out clearly the relationship between ordinary electrocardiograms and vectorcardiograms and some of the problems relating to the registration of the latter. If these matters are clearly understood, much of the uncertainty regarding the clinical value of vectorcardiograms, expressed by some, as well as the overenthusiasm relative to their diagnostic value displayed by others should disappear.

In the simplest possible terms, vectorcardiograms are only a different technic for displaying electrical information contained in two electrocardiograms of the conventional type. The idea is not new, since Einthoven, Fahr, and deWaart[1] in 1913 suggested the use of vectorcardiographic representation of the standard leads, and Mann[2] in 1920 actually constructed from these leads figures that he called monocardiograms. These loops were very similar to vectorcardiograms recorded today in the frontal plane, but his work stimulated little interest and was largely ignored. In 1938 Schellong,[3] in Germany, and Wilson and Johnston,[4] in this country, almost simultaneously described technics for recording electrocardiographic information as vector figures using the cathode-ray oscillograph and the name vectorcardiogram was suggested as a suitable term for these records. Since electrodes on the extremities were used for all of this early work, vectorcardiograms in the frontal plane only were recorded.

The cathode-ray oscillograph is essentially a special type of vacuum tube shaped like an Erlenmeyer flask with a suitable filament or heater emitting large numbers of electrons in the small end or neck of the tube. These electrons are concentrated into a small beam by properly placed, positively charged, focusing electrodes and further accelerated by other positively charged electrodes so the highly concentrated and rapidly moving beam of electrons passes from the small neck of the tube and strikes the inside surface of the larger circular base of the tube near its center. This inner surface is coated with special materials that emit visible radiation, usually blue or green, as a result of the bombardment with electrons. Thus, if the electron beam is in its normal position, at the central axis of the tube, it will cause a brilliant blue or greenish spot to appear at the center of the base of the tube. If the tube is to function as a recording instrument, two sets of deflecting plates (or in some tubes coils of insulated wire to create a magnetic field) must be mounted centrally beyond the electrodes that accelerate the electrons. These plates are at right angles to each other, one set, the vertical plates, being placed above and below the centrally located electron beam and the horizontal plates on each side of the beam. Voltages impressed on the horizontal plates cause the electron beam to be deflected to the right or left, thus causing the spot of light on the face of the tube to move from its central position to the right or left. Similarly, voltages on the vertical plates cause the spot

From the Heart Station, University of Michigan Medical Center, Ann Arbor, Michigan.

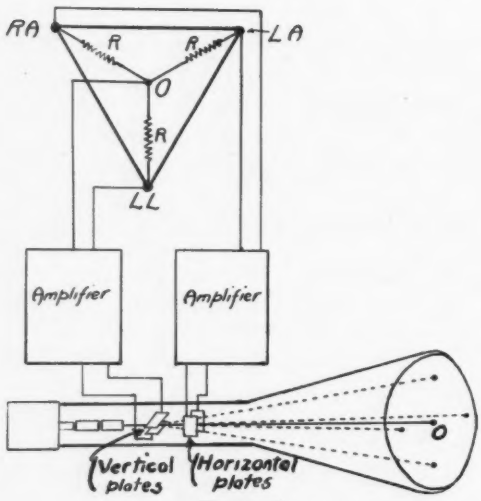

Figure 1

Diagram of cathode-ray tube (below). The heater, focusing and accelerating electrodes are shown at the left, in the neck of the tube, and the vertical and horizontal deflecting plates are seen to the right of these elements. Only transverse and vertical movements of the bright spot from its central position (0) on the face of the tube are shown, although the circuits shown (above) illustrate the technic for recording a vectorcardiogram in the frontal plane. The plates labeled vertical are oriented horizontally but are called the vertical plates because voltages impressed on them cause the electron beam to move up *or* down *and hence the designation "vertical" plates.*

to move either up or down from the central position. Figure 1 illustrates these matters.

The cathode-ray oscillograph is not a very sensitive recording device, and if the instrument is to be employed to record the small voltages involved in the electrocardiogram, these voltages must be stepped up with suitable electronic amplifiers, providing voltage amplification of 50,000 or more. If this is done and amplified lead I is connected to the horizontal plates, with the polarity arranged so an upward deflection in this lead causes the spot to move to the observer's right, and amplified lead V_F (or aV_F), with proper sensitivity, is connected to the vertical plates, so an upward deflection in this lead causes the spot to move downward from the central position, a series of closed loops that represent the vectorcardiogram in the frontal plane will be traced by the bright spot on the face of the tube. These figures are easily photographed if a camera is set up in front of the tube and the shutter is opened for a single heart beat.

It should be clear that a vectorcardiogram obtained by the use of the cathode-ray oscillograph will contain no information not previously available, since it is derived by the combination of two leads (for example, I and V_F), which are commonly recorded as ordinary (scalar) electrocardiograms. Furthermore, although the cathode-ray technic provides an elegant and "automatic" method of obtaining vectorcardiograms, the records would be no different from those constructed from ordinary leads by methods similar to those described by Mann.[2]

Since the deflecting plates in the cathode-ray tube are located at right angles to each other and voltages impressed on either the horizontal or vertical plates cause the electron beam to move in a strictly horizontal or vertical direction, it seems logical, when one wishes to record a vectorcardiogram in the frontal plane, to employ leads or lead systems that provide the best possible transverse and vertical components of cardiac voltages. Similarly, for a vectorcardiogram in the horizontal plane one should employ leads that give transverse and sagittal components of cardiac voltages in pure form; and, for vectorcardiograms in the sagittal plane, leads satisfactory for the vertical and sagittal components of cardiac e.m.f.s. are desirable. From the above, it will be observed that only *three* leads, each giving the transverse, vertical, and sagittal components of heart voltages in pure form, are needed to record satisfactory vectorcardiograms.

By all odds, the biggest technical difficulty in vectorcardiography today is the lack of agreement concerning leads or lead systems that should be employed for their registration; until decisions, which are generally accepted, are made on this important point, standardization of technic as has been attained with ordinary (scalar) electrocardiograms will be impossible.

As mentioned earlier, the vectorcardiograms in the frontal plane taken in 1938 by Wilson and Johnston[4] were obtained by using lead I for the transverse (x) and V_F for the vertical (y) component (fig. 1). In the light of current knowledge, it is clear that these records were not very accurate, primarily because lead I does not give pure representation of the transverse components of cardiac voltages. Duchosal and Sulzer[5] a few years later began to record vectorcardiograms not only in the frontal but in the transverse and sagittal planes as well, and constructed wire models from these figures that depict fairly well the size, shape, and relationship of the loops that represent the P waves, the QRS complexes, and the T waves. Although the rectangular lead system chosen by Duchosal seemed a reasonable and good one at the time, studies in recent years indicate that this arrangement, as well as the closely related cube system used extensively by Grishman and Scherlis[6] and many others in this country in recent years, do not provide good transverse, vertical, or sagittal components of voltages arising in the heart. If the excellence and accuracy of vectorcardiograms are judged on the basis of how good are the orthogonal leads that one employs to obtain them, it must be conceded that vectorcardiograms taken with the cube and related systems are not very satisfactory. This situation has done little to dampen the enthusiasm of some vectorcardiographers who have claimed that their vectorcardiograms are better than ordinary scalar electrocardiograms for the diagnosis of bundle-branch block, ventricular hypertrophy, and other cardiac conditions. Claims of this kind deny the long years of clinical and experimental experience that underlie proper interpretation of ordinary electrocardiograms and are largely nonsense, in the opinion of the writer. Vectorcardiographers should always remember that the vectorcardiograms they record always represent the combination (by the magic of the cathode-ray tube) of two leads from each of which ordinary electrocardiograms may be taken, and further that there can be no essential information in the vector figures that may not be gleaned from a study of these two electrocardiograms. Few of the vectorcardiographers who extoll the value of their vector records would brag about the excellence of electrocardiograms taken *with the same leads.* Most physicians are "suckers" for complicated and fancy equipment, and the writer suspects that much of the current popularity of vectorcardiography arises from the glamorous apparatus, rather than from any well-founded conviction that vectorcardiography represents a truly new approach to electrocardiographic diagnosis.

Burch and associates[7] and others have taken many vectorcardiograms in the frontal, transverse, and sagittal planes, using the equilateral tetrahedron as the basis of their lead system. This arrangement employs lead I for the transverse (x) component, V_F (or aV_F) for the vertical, (y), component, and a point in the back (V_B) behind the heart, and the central terminal as the sagittal (z) component. Of these three leads, only V_F(y) is a good orthogonal lead, and V_B, the sagittal lead, is especially poor. Again, if one believes (with the writer) that vectorcardiograms are only accurate if good orthogonal leads are used to record them, it must be concluded that vector figures taken with the equilateral tetrahedron system are not good records, and conclusions drawn from them (like those from the cube system) must be taken with a large "grain of salt."

This discussion brings up an obvious question. Are there any good and practical systems for obtaining orthogonal leads that may be used to record accurate vectorcardiograms? The answer to this question is a qualified yes. Schmitt and Simonson[8] and Frank[9] have carried out extensive studies on torso models of human subjects and from these investigations have been able to design lead systems that provide orthogonal leads giving far better and purer representations of the transverse (x) and sagittal (Z) components of the cardiac voltages than in any of previously described arrangements. A good vertical component (y) is easy to obtain compared with the other two, and most workers will agree that V_F (or aV_F)

or a lead obtained by electrodes on the left leg and around the neck are quite acceptable. The systems suggested by Schmitt and Simonson and by Frank are both based on experiments in which hearts of normal size and usual location were assumed and the electrode locations and size of resistances in the associated averaging networks were chosen in accord with experimental results in this average "normal" subject. One may therefore properly question the accuracy of these orthogonal leads in patients with considerable cardiac enlargement or an unusually placed heart.

Burger and van Milaan[10] laid the foundations for a great deal of important work on electrocardiographic leads when they described the concept of the lead vector in 1946. Burger[11] more recently has suggested the use of relatively simple lead systems for the orthogonal (x, y, and z) leads by employing coefficients that may be used to correct the error inherent in these leads and make them essentially orthogonal. Unfortunately, the magnitude of these coefficients should vary in different patients with variations in the size and position of the heart, just as should the ideal positions for electrodes and the character of the resistance networks in the systems of Frank and Schmitt mentioned above.

It seems to the writer that a concept closely related to the lead vector, namely that of the lead field, described by McFee and Johnston,[12] points the way to a simple practical scheme for obtaining good orthogonal leads. As mentioned above, either lead V_F (or aV_F) or a bipolar lead with electrodes on the left leg and around the neck provides an entirely satisfactory lead for the vertical component (y) of voltages arising in the heart. This is true because the lead fields associated with these leads could be represented by lines of current flowing uniformly in a vertical direction through the heart. Similarly, leads providing good transverse (x) and sagittal (z) components of cardiac voltages should be associated with uniform lead fields having strictly transverse and sagittal directions. An arrangement consisting of uniformly spaced electrodes (16 or more) mounted on a thin flexible plastic sheet placed over the cardiac area anteriorly and on the posterior chest wall behind the heart should give a uniform, sagittally directed lead field and therefore be a good lead for the sagittal (z) component of cardiac voltages. Each of the electrodes of the grid must be connected through equal, large (1 meg. ohm) resistances to a common terminal, and these terminals, one anterior and one posterior, are the points of connection for the sagittal lead. Reynolds and associates[13] have discussed the technic for a sagittal lead of this kind in detail. A similar multiple electrode arrangement placed on the left and right lateral chest walls at the cardiac level or corrected lead I described by McFee and Johnston[12] should provide a good lead for the transverse (x) components of heart voltages.

It is likely that electrocardiograms or vectorcardiograms taken with the systems of Schmitt or Frank would be much like those obtained by the multiple electrode arrangement outlined above in the majority of patients. It seems to the writer, however, that since the latter system does not depend on fixed positions for electrodes and an accompanying network of resistances tailored to fit an average normal subject, it has some advantages over the systems proposed by Schmitt and by Frank. For example, if a patient is known to have a greatly enlarged heart the only important consideration with the multiple electrode system is to be sure that the grid arrangement is large enough to cover the projected area of the heart for both sagittal and transverse leads. Objections to the use of the grid system because it is complicated and time consuming are not justified by the facts, since it has been satisfactorily used in our laboratory by technicians trained only in the registration of routine electrocardiograms.

A great many studies have been carried out to estimate the comparability and excellence of some of these systems for orthogonal leads, and there seems to be general agreement that the arrangement of Schmitt and Simonson (S.V.E.C.III), the seven-electrode system of Frank, and the multiple electrode grid set-up give similar results and are clearly superior

to the cube or equilateral tetrahedron systems. Nevertheless, as mentioned earlier, there has been no general agreement on which plan should be accepted, and until this is achieved vectorcardiography will continue to be an impirical and mixed-up science.

An important additional reason for uniform acceptance of good arrangements for orthogonal leads is that leads good for vectorcardiography would also be good for ordinary scalar electrocardiograms and should simplify routine electrocardiographic technic greatly. Thus, it is almost certain that two leads giving complete and accurate representations of the transverse and vertical components of cardiac voltages would provide all the information now recorded in six limb leads. It is also likely that, for many purposes, a good sagittal lead would give the essential data displayed by the six routine chest leads. Thus, in three leads one would find a display of the essential electrical activity of the heart, and these could be used either for ordinary scalar electrocardiograms or for vectorcardiograms, as the physician desired. If it is remembered that a good orthogonal lead rejects voltages in the heart that are not oriented in a certain direction (transverse, vertical, or sagittal) but serves to sum up or average all components of heart voltages in one of these directions, it should be clear that the electrical effects of a small lesion, like an anterior infarct, might be lost in the averaging process, and evidence pointing to a lesion of this kind might not appear in a single sagittal lead. Another way of saying essentially the same thing is that not all of the information to be gleaned from leads taken on the surface of the body can be due to a single equivalent dipole located in the heart. Most well-informed workers on electrophysiology of the heart will agree with this view, and it means that three "perfect" orthogonal leads may have to be supplemented by a few chest leads to pick up small lesions, like anterior infarcts, in some patients. This will be equally true whether scalar electrocardiograms or vectorcardiograms are taken with these perfect orthogonal leads.

In the foregoing discussion emphasis has been placed on the fact that vectorcardiograms are only a different way of presenting data readily available in ordinary scalar records and that they therefore can represent no basically new approach to electrocardiographic diagnosis. Nevertheless, vectorcardiograms are much more illustrative of electrical events occurring in the heart than are scalar electrocardiograms, and they depict very clearly phase differences between peaks of R waves (for example) that can only be appreciated if the scalar ingredients of the vector figure are recorded simultaneously. These matters have been discussed and are illustrated in an editorial written by the writer several years ago.[14]

For example, if one examines a normal vectorcardiogram taken in the frontal plane (fig. 2A), it is immediately clear that during excitation of the ventricles (represented by the QRS loop) the average direction of excitation is downward and to the left, close in direction to the anatomic long axis of the heart, and that there is not a great deal of rotation of the instantaneous electrical axes during the entire period of activation. Further, one sees the normal relationship between the T loop and the QRS loop. The figure representing the P wave is also seen in most vectorcardiograms but without greater amplification than is ordinarily employed these loops are small and often obscured in the central (zero) spot. The loops representing P waves are not shown in figure 2.

The vectorcardiogram on the same normal subject taken in a transverse or horizontal plane is shown in figure 2B. Here it will be observed that early in excitation of the ventricles the vectors are small and directed anteriorly and slightly to the right corresponding, of course, to the small initial R waves seen in the right precordial leads, but as activation progresses the vectors rotate in a counterclockwise rotation to assume a posterolateral and finally a nearly posterior direction. These later vectors are responsible for the large S in right precordial and the R waves in left precordial leads. It will also be seen that

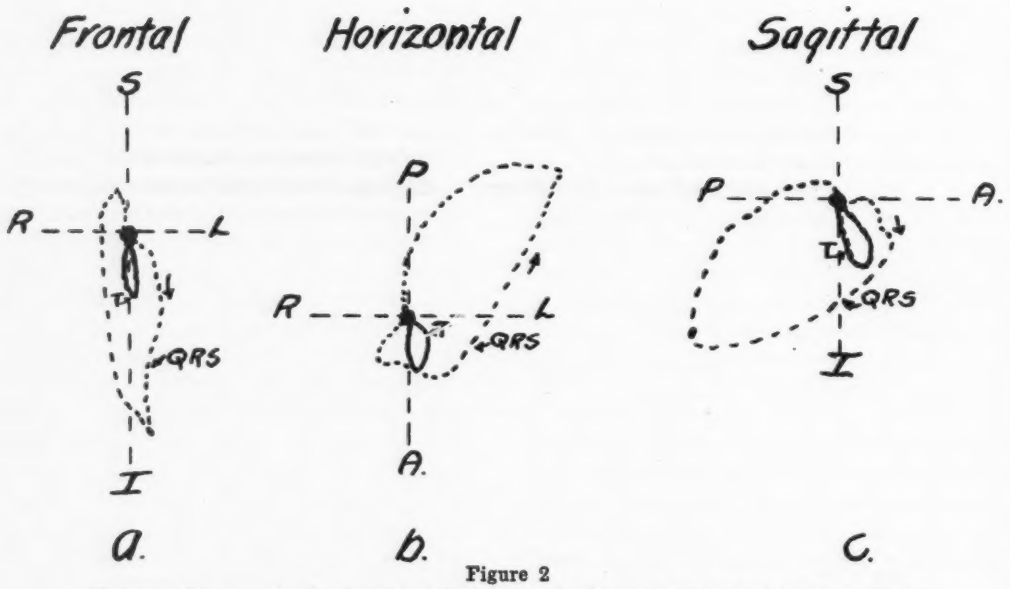

Figure 2

Vectorcardiograms in the frontal, (a), horizontal, (b), and sagittal, (c) planes. These were traced from records recorded from a normal subject with use of the multiple electrode (grid) arrangement. Orientation of the figures is made clear by indices on the axes, thus R, right; L, left; S, superior; I, inferior; A, anterior; P, posterior.

the vectorcardiogram, again of the same normal subject, in the sagittal plane (fig. 2C) may be similarly interpreted.

There has been considerable confusion about the term "spatial" vectorcardiography. Many workers would say that the writer is a "spatial" vectorcardiographer, since he has presented the data shown in figure 2. This is not strictly true, however, since all this figure shows is the projection of the loops of the true spatial vectorcardiogram on three planes mutually perpendicular to each other. It is true that any two of these three vector figures provide the information necessary to visualize (if one is imaginative) the approximate outline and position of the loops in three-dimensional space, and if one is industrious, as Duchosal, Burch, and associates, and others have been, to construct wire models of the loops as they exist in space. If these models are carefully made, they are of considerable interest and importance, because from them vectorcardiograms in any desired plane may be obtained by projection, and from these vectorcardiograms scalar electrocardiograms may be derived by projection on the line of any desired lead. The stereovectorelectrocardiograph (SVEC) described by Schmitt[15] is a technic for the visualization of the spatial vectorcardiogram and accomplishes the same end as is achieved by the wire models mentioned above. Unfortunately, the cost and complexity of the equipment required limit the usefulness of this instrument.

This discussion should make it clear that the clinical value of vectorcardiograms should depend primarily on the character of the leads employed to record them. Since the deflecting plates in the cathode-ray tube are placed at right angles to each other and movements of the electron beam and therefore the spot of light on the face of the tube can only move in strictly transverse or vertical directions from the center of the tube when voltages are placed across the horizontal and the vertical deflecting plates respectively, it seems essential to the writer that components of cardiac voltages at right angles to each other (i.e., orthog-

onal leads) of the purest possible kind should be selected for the registration of vectorcardiograms. It must be pointed out that vectorcardiograms will be obtained if any two different leads are amplified and impressed on the horizontal and vertical plates of the tube, but these will *not* be in the frontal, horizontal, or sagittal planes unless good orthogonai leads are chosen. Workers can go on almost indefinitely collecting vectorcardiographic data using poor (not orthogonal) leads and attempting to correlate these with other clinical and postmortem findings. Much activity of this kind has been carried out and unfortunately fortuitous circumstances have occasionally led some individuals to believe that such vector records are more accurate and reliable than are ordinary scalar electrocardiograms.

It must be remembered that satisfactory orthogonal leads have been developed only in recent years to meet the requirements inherent in a good technic for vectorcardiograms and that no one has had much experience with such leads for the registration of ordinary scalar electrocardiograms. It will be difficult for many physicians, including the writer, to drop the time-honored limb leads and the "unipolar" extremity and chest leads in favor of three orthogonal leads, supplemented occasionally by a few chest leads of the type now recorded. Nevertheless, it seems almost certain that the simplicity of a rectangular (orthogonal) reference system and that many other advantages of good orthogonal leads will lead eventually to their general acceptance for routine clinical work. When this time arrives, vectorcardiograms may be recorded if the physician likes the vector method and has the necessary equipment. A few scalar tracings will probably always be necessary for measurement of important intervals in the electrocardiogram, especially the P-R interval, and for diagnosis of arrhythmias. A number of individuals have suggested and have actually recorded vectorcardiograms on slowly moving paper or film, and this does provide a horizontal time axis for the vector records. This technic, however, has the disadvantage of distorting the vectorcardiograms.

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ABSTRACTS

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ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Blakemore, W. S., Zinsser, H. F., Kirby, C. K., Whitaker, W. B., and Johnson, J.: Pericardiectomy for Relapsing Pericarditis and Chronic Constrictive Pericarditis. J. Thoracic Surg. 39: 26 (Jan.), 1960.

The thesis of this report is a plea for surgical intervention with removal of the diseased pericardium prior to the development of scar tissue sufficient to reduce the efficiency of the cardiac mechanism. This form of therapy is not suggested for the case of acute pericarditis but rather for the relapsing case, even in the absence of cardiac constriction or tamponade. It is emphasized that surgery can be performed with greater ease at this stage. In 28 patients with chronic constrictive pericarditis treated surgically there were 3 deaths. The deaths occurred in patients with longstanding heart failure. In 8 patients with relapsing pericarditis there were no deaths and 100 per cent of the patients returned to work. It is noted that the procedure was much simpler in the latter group. Wide resection of the pericardium is done and the epicardial layer is removed from the ventricles when necessary. Removal of the constricting tissues over the ventricles appears to be most important. In the group of patients classified as relapsing pericarditis the average duration of symptoms was 5 months and the average number of hospital admissions necessary was 3. No specific etiology was found in any of the 8 patients with relapsing pericarditis, and in only 4 of the 28 patients with chronic constrictive pericarditis was tuberculosis the causative agent. The mechanism by which removal of pericardium interrupts the disease is not known. It must be remembered that the myocardium is involved in these patients. Therefore overhydration is avoided in the postoperative period and activity must be limited for the first month.

LEVINSON

Lisan, P., Uricchio, J. F., Marino, D. J., Deshumukh, M., and Likoff, W.: Staphylococcal Endocarditis. Am. Heart J. 59: 184 (Feb.), 1960.

The records of the Hahnemann Medical College and Hospital, Philadelphia, for the years 1949 to 1958 yielded 38 cases of staphylococcal endocarditis. Of these, 31 patients had rheumatic heart disease and 5 were suffering from congenital heart disease. Twenty-one patients had had cardiac surgery within a year prior to the development of endocarditis. The clinical data afforded by this study are presented. Significant were the observations not only of an increase in the incidence of staphylococcal endocarditis in the past 5 years, but also of an increase in the mortality rate due to lack of response to antibiotic therapy. In treatment penicillin was found to be the most valuable antibiotic, but other antibiotics which could be used synergistically with penicillin were also required. In 2 patients cure was obtained only when a focus of staphylococci was found and removed.

SAGALL

Murnane, T. G., Craighead, J. E., Mondragon, H., and Shelokov, A.: Fatal Disease of Swine Due to Encephalomyocarditis Virus. Science 131: 498 (Feb. 19), 1960.

This report deals with an outbreak of encephalomyocarditis virus among swine in which approximately 30 pigs died over a 20-day period. The general appearance of the pigs was good. In 1 instance an animal suddenly collapsed in severe dyspnea and died within a few minutes. At autopsy, hydrothorax, hydropericardium, and ascites were frequently observed. The lungs showed congestion, edema, and some consolidation. The heart was soft and pale with minute yellowish areas suggestive of necrosis. On microscopic examination severe myocarditis with round-cell infiltration, vascular congestion, edema, and degeneration of the myocardial fibers was noted. In addition, meningitis and spotty neuronal degeneration were observed. The encephalomyocarditis virus was isolated from the organs of these pigs. After passage through mice the disease could be reproduced in swine by inoculation of pigs with this virus injected intercerebrally or intraperitoneally. Myocardial failure appeared to be the primary cause of death and the outstanding lesion was a severe myocarditis. The virus strain was re-identified from these inoculated pigs. This virus has been implicated as a cause of human disease. The association of this virus with disease in domestic animals has apparently not been previously reported.

LEVINSON

Uglov, F. G.: Diagnosis and Surgical Treatment of Constrictive Pericarditis. Surgery 47: 247 (Feb.), 1960.

The author's experience in the surgical management of constrictive pericarditis is reviewed. He stresses the importance of removing as much of the thickened pericardium as possible, including the areas surrounding the large vessels, atria, and apex. Acute dilatation of the heart occurred postoperatively in some patients. The author recommends a sternal-costal flap technic and a transbipleural approach. This technic is described in detail.

SHEPS

HYPERTENSION

Dollery, C. T., Shackman, R., and Shillingford, J.: Malignant Hypertension and Hypokalaemia: Cured by Nephrectomy. Brit. M. J. 2: 1367 (Dec. 19), 1959.

Two patients with malignant hypertension and hypokalemia of rapid onset are presented. Despite a low serum level of potassium, they had constant renal loss of potassium. Renal artery obstruction was demonstrated in each case, and hypertension was cured in one by nephrectomy, though, in the other, only a slight reduction in blood pressure was obtained. In both cases, however, the serum potassium level after operation has remained normal without supplements. Unilateral renal ischemia may cause hypokalemia through several different mechanisms. One method is the loss of potassium from the damaged tubules of the ischemic kidney. However, loss from the contralateral kidney due to nephrosclerosis of malignant hypertension or to a humoral factor, such as secondary hyperaldosteronism, could also account for potassium loss. Since nephrectomy resulted in normal serum potassium levels in these patients, primary hyperaldosteronism could be ruled out.

KRAUSE

Haas, E., and Goldblatt, H.: Renin Content of Kidneys in Experimental Renal and Human Essential Hypertension. Am. J. Physiol. 197: 1103 (Nov.), 1959.

The renin content of the ischemic kidney of dogs with experimental renal hypertension due to constriction of only 1 main renal artery was significantly elevated, while that of the contralateral, untouched kidney was abnormally low. Constriction of the main artery of 1 kidney and contralateral nephrectomy also resulted in hypertension and a great increase of renin in the ischemic kidney. In patients with hypertension accompanied by impairment of renal excretory function the renin content of the kidneys, the seat of arterial and arteriolar sclerosis, with or without accompanying pyelonephritis, was increased, on an average, to about 4 times that of normal kidneys, and, in individual cases, to as much as 16 times the mean normal value. In this study, extraction of the renal tissue, after the freezing and thawing of the organ, yielded twice as much renin as previous extraction of the fresh tissue. The specific activity of the renin preparations from dog and human kidneys was enhanced twofold and fourfold, respectively, by means of revised methods for the extraction and partial purification of renin.

KAYDEN

Holstein, J.: Influence of Ganglionic Blocking Agents on Plasma Volume and Extracellular Space. Ztschr. Kreislaufforsch. 48: 1014, 1959.

In 8 persons with normal blood pressure and in 6 with hypertension the plasma volume was determined according to the method of Clausen with Evans-blue dye and the extracellular space determined according to the method of Roe, Epstein, and Goldstein. Measurements were obtained in the horizontal position and after tilting at 45°. Without drugs, tilting had little effect on these values. After the intravenous injection of hexa-

methonium or diamonal, tilting caused a decrease of plasma volume and an increase of extracellular space. The changes are interpreted as due to fluid shift from intravascular to extravascular spaces.

LEPESCHKIN

Miall, W. E.: Follow-up Study of Arterial Pressure in the Population of a Welsh Mining Valley. Brit. M. J. **8**: 1204 (Dec. 5), 1959.

During 3 months of the winter 1953-54 arterial blood pressures were recorded in a random sample of the population of a Welsh mining valley. Under exactly comparable conditions the survivors of the original population were similarly studied during the same 3 months of the winter during 1957-58. The results suggest the possibility that arterial pressure may be increasing in middle-aged males, particularly those previously engaged in heavy jobs. In the original study it was observed that childless men and women had higher blood pressures than their counterparts with children. These observations were further confirmed by the fact that increases in pressure were less in those subjects who had children during the 4-year period. Women with large salt appetites in general had lower blood pressures and smaller pulse pressures and were lighter than women whose salt consumption was lower.

KRAUSE

Peart, W. S.: Hypertension and the Kidney. I. Clinical, Pathological, and Functional Disorders, Especially in Man. Brit. M. J. **2**: 1353 (Dec. 19), 1959.

Unilateral renal disease is the main curable form of renal hypertension and, in particular, this applies to unilateral renal artery obstruction. It is not widely appreciated, however, that in man it is possible to have quite gross renal failure without a concurrent rise in blood pressure in the presence of tubular necrosis alone. But when renal cortical necrosis is found, hypertension is very common. Irradiation nephritis can also produce hypertension. In pyelonephritis, the associated hypertension is probably related to partial or complete arterial obstruction. Renal biopsies do not consistently reveal arteriolar obstruction in early hypertension, which is evidence in favor of the concept that the hypertension is responsible for the subsequent changes in renal blood flow. By far the commonest cause of renal artery obstruction is atheromatous change in the artery usually close to its origin from the aorta. This should be investigated as the etiologic factor for the hypertension when the following features are applicable: severe hypertension with no other demonstrable cause at any age; rapid progression of benign to malignant phase; history of other vascular occlusions; loin pain with fever and leukocytosis, especially in the presence of a source of emboli; polyuria and proteinuria; and murmur over the abdomen. It is re-emphasized that a normal pyelogram may be obtained in the presence of stenosis of a renal artery. Generally the urine flow and sodium concentration on the side of renal artery stenosis are diminished. Numerous surgical procedures to correct the stenosis are available and the type of procedure will vary with the local condition. Nephrectomy is for the badly damaged kidney, while the other procedures are used to meet the pathologic and anatomic situation.

KRAUSE

Peart, W. S.: Hypertension and the Kidney. II. Experimental Basis of Real Hypertension. Brit. M. J. **2**: 1421 (Dec. 26), 1959.

The experimental basis of renal hypertension is covered from many aspects. These include the failure of the kidneys to excrete or destroy an extrarenal pressor substance, the failure to produce a vasodilator, increased responsiveness of normal pressor mechanisms, decreased response of baroreceptors, stimulation of some extrarenal pressor system, redistribution of electrolytes and water, and the production of a vasoconstrictor. There appears to be no consistent relationship between the level of the blood pressure and the histopathologic anatomy of the kidneys in hypertension. In man the ischemic change in the tubules is not uniform nor is it paralleled in the experimental animal. In man arterial obstruction to 1 kidney and in animals the Goldblatt kidney can lead to hypertension. If the arterial obstruction is properly removed by reconstruction of the artery or if the kidney beyond the obstruction is removed the blood pressure may return to normal. Proper investigation of renal function must always be accomplished before over-enthusiastic surgery is performed on the basis of renal arteriography. Critical analysis is made to distinguish changes which occur as a consequence of hypertension as opposed to those which may have a causal relationship. The author cites his experiments in man and animals (rabbits) from which he concludes that renin cannot be wholly, if at all, responsible for the type of hypertension studied, namely that of renal artery obstruction.

KRAUSE

Remington, R. D., Lambarth, B., Moser, M., and Hoobler, S. W.: Circulatory Reactions of Normotensive and Hypertensive Subjects and of the Children of Normal and Hypertensive Parents. Am. Heart J. **59**: 58 (Dec.), 1959.

Vascular reactivity was studied in a group of hypertensive and normal subjects by means of

postural change, cold immersion, breath holding, and exercise. No consistent differences in response were noted in 10 normotensive, 10 labile hypertensive, and 9 fixed hypertensive adults. In 50 children of hypertensive parentage there was no evidence of unusual vascular hyperreactivity as compared with the responses observed in 50 children of normal subjects. As compared to the children of normal subjects, those with hypertensive parents showed a significantly higher mean systolic blood pressure and a significantly lower pulse rate, but the mean diastolic pressure of the 2 groups did not differ. It is concluded that although a high "normal" systolic blood pressure may be found at puberty in certain offspring of hypertensive parents, the conventional tests of vascular reactivity are not useful in determining those who are likely to develop hypertension.

SAGALL

van Proosdij-Hartzema, E. G., Akkerman, A. M., and de Jongh, D. K.: A New Hypotensive Agent Derived from Serpentine. Arch. Int. pharmacodyn. **123**: 168 (Dec.), 1959.

A series of analogs of serpentine—the methylester of serpentinic acid—was prepared. Some of these were found to be more potent hypotensive agents than serpentine in normal rats and in rats with experimental renal hypertension. Ph. 458, the isobutyl analog, was selected because this substance combined potent hypotensive activity with a relatively low toxicity. Unlike reserpine, Ph. 458 lowered the blood pressure in all active dosages and did not mobilize epinephrine. Ph. 458 lacked the sedative activity characteristic of reserpine.

BRACHFELD

Walker, C. H.: Migraine and Its Relationship to Hypertension. Brit. M. J. **2**: 1430 (Dec. 26), 1959.

A family history of migraine and hypertension is common to patients with these diseases. Furthermore the personality structure of the 2 disorders has several points in common such as suppressed emotional conflict and psychoneuroses. In both situations headaches are presumably produced by dilatation and distention of the cranial arteries. Among 5,785 patients in his general practice the author found an incidence of 4.85 per cent with migraine headaches. Of these patients 54.8 per cent gave a family history of migraine. Patients with migraine had a higher blood pressure than the average. In patients over the age of 50 there was a clear correlation between migraine and essential hypertension. The incidence of migraine rose as the level of blood pressure increased.

KRAUSE

Yates-Bell, J. G.: Nephrectomy in Cases of Hypertension. Brit. M. J. **2**: 1371 (Dec. 19), 1959.

The literature on nephrectomy for hypertension is reviewed and an optimistic attitude is assured. Certain criteria for patient selection are outlined: the blood pressure must be labile; intravenous pyelography should attach suspicion to 1 kidney; on the suspected side, urine separation should reveal delay in indigo carmine excretion and lowered urea and sodium concentrations; aortography should reveal lesions of the renal blood vessels. Sixty-six of 89 cases of nephrectomy for unilateral renal disease in hypertension were selected. A 45.5 per cent cure was claimed, based primarily on the maintenance of a diastolic blood pressure level of 90 mm. Hg for 1 year postoperatively. In general, patients over 50 years of age seldom benefited unless the hypertension was recent in origin and the younger the patient the better the results.

KRAUSE

PATHOLOGY

Bergman, R. A.: A Note on the Fine Structure of the Turtle Heart. Bull. Johns Hopkins Hosp. **106**: 46 (Jan.), 1960.

The atria and ventricles of the turtle heart were carefully studied histologically in an attempt to define the specialized conducting system. When the water soluble particulate matter in the subsarcolemmal and interfibrillar spaces was removed, the sarcolemma was seen to be intimately connected to the Z lines of the myofibrils. An organized system of tubules and vesicles similar to the sacroplasmic reticulum of other species was found to be lacking. These observations suggested that the carrier for the interval activation of the myofibrils in the turtle heart is probably related to the structure of the Z line and to the interfibrillar connections that link adjacent Z lines to each other.

KARPMAN

Lumb, G., and Shacklett, R. S.: Human Cardiac Conduction Tissue Lesions. Am. J. Path. **34**: 411 (Apr.), 1960.

Gross and histologic examinations were conducted on 260 human hearts obtained at necropsy; extensive examinations were carried out on 35 of the hearts in which there were significant lesions of the conducting tissue. "Sudden death" (abrupt death or death occurring within 5 to 6 hours after hospitalization) occurred in 25 of the patients; in 13 of these individuals, pathologic processes existed that might have led to sudden death. It was therefore impossible to assess the significance of the conduction tissue abnormalities that were present. In the remaining 12 patients, however,

there was considerable suspicion that a conduction tissue lesion was the precipitating factor in the sudden demise: 3 patients had extensive myocardial calcification; 3 patients had myocarditis; 2, cardiac amyloidosis, 1 had an unexplained hemorrhage into the atrioventricular node and bundle of His, another patient had a recent infarct in the intraventricular septum, evidence of Aschoff body formation was present in yet another patient, and a fibrotic lesion was found in the conduction tissue of the last patient who suffered cardiac arrest during surgery. In all of these 12 patients, no extracardiac cause of death was found at necropsy. Of the 35 patients, 26 had had premortem electrocardiograms; tracings in 19 of these patients revealed either bundle-branch block or some degree of atrioventricular dissociation.

KARPMAN

Short, D. S., and Thomson, A. D.: The Arteries of the Small Intestine in Systemic Hypertension. J. Path. & Bact. 78: 32 (Oct.), 1959.

Arteriographic and histologic postmortem studies were performed on the arteries of the small intestine of 13 control cases and 9 cases of established hypertension. The salient finding consisted of a diffuse narrowing of the submucosal arteries in the hypertensive cases, despite the fact that the mean caliber of the mesenteric arteries was unchanged (even though the mesenteric vessels were more tortuous and displayed more intimal thickening than the controls). The narrowing was not due to intimal thickening nor to medial hypertrophy but rather due to unidentified structural changes that produced decreased arterial distensibility. The authors concluded that the process is probably similar to that seen in the peripheral arteries of the lung in pulmonary hypertension. The evidence suggested that arterial contracture is at first a result of hypertension and, having once developed, tends to perpetuate the hypertension. Of interest was the observation that the 1 case of established hypertension with a normal submucosal arterial pattern had a severe proximal stenosis of the stem of the superior mesenteric artery.

KARPMAN

Stehbens, W. E.: Focal Intimal Proliferation in the Cerebral Arteries. Am. J. Path. 36: 289 (Mar.), 1960.

Serial sections of the cerebral arteries were obtained from 22 human subjects ranging in age from a fetus of 28 weeks to an infant of 8 months. Intimal pads about the bifurcations of the arteries were preceded by and associated with prominent elastic-tissue changes. These elastic-tissue changes were thought to be degenerative in nature due to some damaging factor, possibly eddy currents. The author hypothesized that the intimal pad proliferation may have been compensatory to the loss in tensile strength secondary to the elastic-tissue changes. Facial and dorsal pads preceded the lateral angle and the apical pads in formation and were found to consist primarily of musculo-elastic tissue.

KARPMAN

Wennemark, J. R., Benvenuto, R., and Lewis, F. J.: Destruction of the Specialized Conduction Tissue in the Live Canine Heart with Iodine. J. Thoracic Surg. 39: 137 (Feb.), 1960.

It has been suggested that iodine solution be used as a supravital staining method in clinical material during open-heart surgery to visualize and avoid traumatic injury to the conductive system. In this experiment 9 medium-sized dogs were anesthetized with intravenous sodium pentobarbital. The area of the right main bundle-branch block was stained by applying a cotton pledget dampened with iodine solution. In all cases the bundle was stained and well visualized. Control electrocardiograms were made in these animals immediately following and again in 14 days, at which time the animal was sacrificed. In 2 cases, just before sacrificing the animal, the left main bundle branch was injured by a probe introduced into the left ventricle through the posterior myocardial wall near the septum. By this method complete right bundle-branch block was proved to be present, for when left bundle-branch block was added, a complete heart block was noted immediately. The conduction system was examined grossly in all dogs after sacrifice. Histologic examination was also performed in 2 dogs. The iodine solutions used in this study were 5 per cent elemental iodine and 10 per cent potassium iodide in aqueous solution (Lugol's solution). The control electrocardiograms in all 9 animals were normal. In 8 cases the immediate tracing following surgery and the 14-day tracing showed a complete right bundle-branch block while in 1 case in which Lugol's solution was used the block appeared to be incomplete. In 7 cases there was severe tissue reaction in the area of application of the iodine solution and in 2 of these this area was covered by a large thrombus. In 1 case the thrombus extended into the pulmonary outflow tract in the proximal main pulmonary artery causing a severe degree of obstruction of this vessel. In 2 cases, in which the endocardial tissue reaction was not so severe, the main bundle branch could be seen as a dense white band in the area stained which was a distinct change from its normal appearance. At the point of application of the solution there was loss of ability of the bundle to stain with

Lugol's solution. Distally, the uninvolved bundle and Purkinje tissue retained the property to be stained with Lugol's solution. In the 2 cases studied histologically the endocardium was inflamed and fibrotic. Some sections showed organizing fibrin on the surface of the endocardium. It is pointed out that the use of iodine solutions to stain conduction tissue supravitally in man should be more carefully evaluated because of the permanent damage which may be produced by this substance in the conduction system of dogs.

LEVINSON

PHARMACOLOGY

Briggs, A. H., and Holland, W. C.: Antifibrillatory Effects of Electrolyte-regulating Steroids on Isolated Rabbit Atria. Am. J. Physiol. **197**: 1161 (Dec.), 1959.

The effects of desoxycorticosterone (DOC) and a new synthetic steroid-17-spirolactone (SC8109) were determined on the functional refractory periods (FRP) and transmembrane fluxes of potassium in isolated rabbit atria and compared with the effects of quinidine. All 3 agents lengthened the FRP, inhibited the effects of acetylcholine (ACh), terminated or prevented ACh-induced fibrillation and depressed the transmembrane efflux of potassium. Potassium influx was also decreased with higher concentrations of the steroids or after a delay in time. Aldosterone and delta-1-9 alpha-fluorohydrocortisone had no effect on the FRP or potassium fluxes. It was concluded that DOC, spirolactone and quinidine act similarly as antiarrhythmic compounds by depressing sodium entry.

KAYDEN

Fawaz, G., and Tutunji, B.: Oubain-Induced Ventricular Tachycardia and Its Effects on the Performance and Metabolism of the Dog Heart. Brit. J. Pharmacol. **14**: 355 (Sept.), 1959.

In dog heart-lung preparations subjected to Oubain-induced ventricular tachycardia (up to mean rates of 198 per minute) for a period of 1 hour, coronary blood flow increased an average of 171 per cent, oxygen consumption increased an average of 76 per cent, coronary venous blood oxygen saturation increased 31 per cent, and calculated cardiac work did not change significantly. Control preparations showed a similar rise in coronary blood flow, and 11 per cent decrease in oxygen consumption, a doubling of oxygen saturation of coronary venous blood, and a 6 per cent decrease in work performed. Preparations having electrically induced atrial tachycardia (up to mean rates of 202 per minute) showed a 233-per cent increase in coronary flow, a 23-per cent increase in oxygen consumption, a 93-per cent increase in oxygen saturation of coronary venous blood, and no definite change in work performed. It appeared that "therapeutic" doses of oubain did not increase the mechanical efficiency of the heart. "Toxic" doses of oubain did not decrease the phosphocreatine or labile nucleotide phosphorus content of the myocardium provided it did not become hypoxic.

ROGERS

Ford, R. V., and Nickell, J.: Pharmacologic Observations on a More Potent Benzothiadiazine Diuretic (Be. 724-A). Am. Heart J. **59**: 215 (Feb.), 1960.

Pharmacologic studies of an analogue (3-benzyl-3, dihydro-6-(trifluoromethyl) 2H-1, 2, 4-benzathiadiazine-7-sulfonamide, 1, 1-dioxide) in the benzothiadiazine family of oral diuretics are reported. The drug was found to be an effective oral diuretic agent with 2.8 mg. being equivalent to 20.0 mg. of meralluride intramuscularly. Compared to other members of this group of compounds, the drug showed a significantly increased natriuresis and decreased loss of potassium and bicarbonate. It was effective upon continuous administration in a wide variety of edematous and hypertensive states. Its use did not result in significant serum biochemical changes. It is considered by the authors to represent a definite advance in diuretic therapy.

SAGALL

Krück, F.: Clinical Studies on the Mechanism of Action of Some New Diuretics. German M. Monthly **4**: 414 (Dec.), 1959.

In 10 patients with edema of various causes the effect of hydrochlorothiazide was studied. It was found that with daily doses of 50 to 100 mg. of the drug there was a loss of sodium and chloride with a corresponding loss of water. The effect was dependent upon the dose employed. No undesirable reactions were noted, even after prolonged administration. Hydrochlorothiazide proved to be about 20 times more effective than chlorothiazide. The mechanism of its action was discussed and compared with that of some of the other diuretics.

SAGALL

Liot, F., Coblentz, B., Scebat, L., Gras, H., and Lenegre, J.: Preventive Effect of Ephedrine on Syncopal Accidents due to Quinidine (Study of 300 Cases of Regularization of Atrial Fibrillation). Arch. mal. coeur **12**: 1337, (Dec.), 1959.

As most cases of syncope or death resulting from quinidine treatment appear to have been due to conduction block, 0.01 Gm. of ephedrine was given for each 0.3 Gm. of dihydroquinidine to counteract this effect. All patients were given anti-

coagulants and received sufficient digitalis to reduce their ventricular rate to 60-70 before treatment was begun. After a test dose of 0.15 Gm., 0.3 Gm. was given at 2-hour intervals, and the daily dose of 0.9 Gm. was increased 0.3 Gm. every second day until sinus rhythm appeared or a ceiling of 2.7 Gm. was reached. This dose was maintained for 1 day and then decreased in the same way. In 300 treatments carried out in this way, no deaths and only 2 episodes of syncope were observed; whereas in 390 treatments carried out in a similar way but without ephedrine at the same hospital earlier, 7 deaths and 5 bouts of syncope were observed. The smaller percentage of conversions (52 per cent compared to 60 per cent in the earlier series) is attributed to a higher percentage of rheumatic heart disease rather than to an adverse effect of ephedrine. In the one case of sudden death observed after completion of the paper the P-R interval exceeded 0.30 second; such a prolongation of the P-R interval was seen in only 7 of 172 conversions, and was found in 3 of 4 patients with transient syncope. One patient, in whom syncope could be interrupted only by intracardiac epinephrine, had shown nodal rhythm. All these incidents occurred after conversion, when the dose of quinidine was being reduced. Occurrence of P-R prolongation or nodal rhythm accordingly indicated the necessity of increasing the dose of ephedrine and decreasing that of quinidine. Furthermore, accidents can be avoided by not treating patients with marked cardiac enlargement or intractable failure, by daily electrocardiography and interruption of treatment after appearance of multifocal extrasystoles or those appearing in groups.

LEPESCHKIN

Malamos, B., Moulopoulos, S. D., and Dimakis, D.: Catheterization of Coronary Vessels of the Heart; Pressure Measurements and Effect of Drugs. Ztschr. Kreislaufforsch. **49**: 58 (Jan.), 1960.

Catheterization of the coronary arteries from the carotid artery with venous catheters of 1.3 to 1.64 mm. outside diameter could be carried out in 28 of 29 dogs but 6 of the animals died in ventricular fibrillation. Pressures in the proximal portions of the coronary arteries resembled aortic pressure, while those in the distal portions resembled intraventricular pressures. These findings were confirmed in open-thorax experiments by direct puncture of the coronary arteries. Intracoronary injection of strophanthin and calcium gluconate caused increased coronary pressure without changing the heart rate or the aortic pressure and must therefore have a direct specific effect on the coronary arteries. Sympatol increased coronary pressure parallel to aortic pressure, while the effect of aminophylline, atropine, and epinephrine could not be evaluated because of increase of heart rate. Many other drugs were studied with uncertain results.

LEPESCHKIN

Massaro, G. D., Finnerty, F. A., Jr., and Ryan, M.: The Effect of Reserpine and Digitalis on the Heart Rate during Noradrenaline Infusion. Am. Heart J. **59**: 401 (Mar.), 1960.

In 12 normal individuals without cardiovascular disease at least a 13 per cent decrease in heart rate was observed during the infusion of norepinephrine. This response was not significantly altered after either digitalis or reserpine therapy.

SAGALL

Michel, D., Hartleb, O., and Marxhausen, E.: Statistical Clinical Studies on the Action of Digoxin. Ztschr. Kreislaufforsch. **48**: 997, 1959.

In 40 normal persons, 72 cardiac patients without failure and 42 patients with failure, in nearly basal conditions, a large number of circulatory values was determined before, and at 10 to 15-minute intervals during a 3-hour period following the intravenous injection of 0.5 mg. of digoxin. The heart rate, the corrected Q-T duration, the tension and ejection periods (determined from carotid pulse, heart sounds, and electrocardiogram according to Blumberg), the diastolic blood pressure, the venous pressure, the cardiac stroke volume, and work and peripheral resistance (determined according to Wezler and Böger) showed a change in the direction of average normal values, the magnitude of which was proportional to the individual deviation from these values. The more pronounced effect in patients with heart failure was related to the greater deviation from normal values in these patients. The increase in systolic blood pressure was greater in patients without heart failure than in those with failure, whereas the increase in the P-R interval was greater in the latter than in the former. The changes in these two values showed no relation to their deviation from the normal average. In addition to the effect in relation to the deviation from the normal average, increasing age of the patients caused increasing reduction of the tension period, venous pressure, and corrected Q-T duration and an increasing elevation of the cardiac output. Men showed a greater rise in diastolic pressure than women. These relations were found to be statistically significant.

LEPESCHKIN

Robinson, S. J.: Digitalis Therapy in Infants and Children. J. Pediat. **56**: 536 (April), 1960.

Digitalis therapy in infants and children is reviewed in this article. The author discusses the

pharmacology, biochemistry, and physiology and enumerates the various preparations of the drug that are available commercially. Digitalization and maintenance dosage schedules are presented, and both the recognition and therapy of digitalis intoxication are thoroughly discussed. He emphasises that the major value of the digitalis preparations is in the treatment of arrhythmias and congestive heart failure, and he also reviews the supportive measures that should be used in the treatment of these disorders.

KARPMAN

Shapiro, T. R., and Ehrenfeld, E. N.: Paroxysmal Tachycardia in the Newborn. J. Dis. Child. **99**: 248 (Feb.), 1960.

Two episodes of supraventricular tachycardia were terminated by digitalis therapy in a newborn infant in whom no evidence of organic heart disease was detectable. A second newborn infant developed atrial flutter (which proved to be refractory to treatment) and died in congestive failure; pulmonary stenosis and an atrial septal defect were found at necropsy. The authors concluded that in addition to anatomic defects, other factors such as an immature conduction system and neurogenic factors may be operative in these rhythm disturbances. He noted that supraventricular tachycardia, if treated in time, usually carries a favorable prognosis, whereas in atrial flutter the outcome of the disease, even when treated adequately, is mainly determined by the type of associated congenital lesion. Digitalis is the drug of choice and is said to be superior to the mechanical methods (such as eyeball pressure or induction of vomiting); other drugs such as quinidine, Mecholyl and Pronestyl have also been found to be effective in terminating these arrhythmias.

KARPMAN

PHYSIOLOGY

Alanis, J., López, E., Mandoki, J. J., and Pilar, G.: Propagation of Impulses Through the Atrioventricular Node. Am. J. Physiol. **197**: 1171 (Dec.), 1959.

Records taken from the bundle of His and atrioventricular node region of isolated and perfused dogs' hearts showed an action potential (N potential), which appeared after the atrial response and preceded the electrogram of the bundle of His (H potential). The H potential may disappear without affecting the N potential, and the latter may be abolished while the atrial electrogram is still present. These observations suggest that the N potential is generated independently. The temporal course and the time of occurrence of the N potential indicate that it represents the activity of the atrioventricular node. The N potential divides the A-H interval into A-N and N-H latencies. Progressively increasing frequencies of activation of the atrium lengthened first the N-H latency until the H potential disappeared. Higher frequencies lengthened the A-N latency until the N potential also disappeared. In order to explain the experimental findings, it is suggested that there are 2 functional discontinuities, one located between the atrioventricular node and the bundle of His, and the other between the atrium and the atrioventricular node; the first is the most vulnerable for propagation.

KAYDEN

Bayliss, L. E.: The Axial Drift of the Red Cells When Blood Flows in a Narrow Tube. J. Physiol. **149**: 593 (Dec.), 1959.

The mechanics of the flow of fluids through a narrow tube are reviewed in this article. The author caused defibrinated dog's blood to flow through a capillary glass tube and noted that the optical transmittance of a marginal zone became greater. The magnitude of this increase in transmittance and the width of the zone were not related to an increase in the flow but did vary with different samples of blood. At no time was a marginal sheath observed to be free of blood cells. It was, of course, impossible to decide whether the increase in transmittance was due simply to a change in orientation of the red cells or to a decrease in their concentration. The author concluded that axial movements of the red cells (and the formation of a marginal zone of reduced red cell concentration) were quantitatively inadequate to account for the reduction in the viscosity of the blood with increase in the rate of flow.

KARPMAN

Blount, D H., and Meyer, D. K.: Effects of Cardiac Work on Glycogen Fractions of the Heart. Am. J. Physiol. **197**: 1013 (Nov.), 1959.

Trichloroacetic acid soluble (TCA) glycogen and residual glycogen were determined in the left ventricle and interventricular septum of hearts of unfasted male albino rats. Left ventricular hypertrophy and an elevation of blood pressure were produced in rats by coarctation of the abdominal aorta for a period of 5 days. No change in concentration of either cardiac glycogen fraction was found at the end of the 5-day coarctation period. Coarctation of the abdominal aorta for 1 hour failed to alter the glycogen fractions of the left ventricle, whereas complete ligation of the aorta for the same time interval promoted the deposition of TCA glycogen. In rats subjected to 5, 15, and 60 minutes of swimming, left ventricular glycogen was significantly depleted. Residual glycogen re-

synthesis was complete after 1 hour of rest from 15 minutes of exercise, and the TCA fraction was significantly increased at this time. The method of sacrifice influenced the concentration of the cardiac glycogen fractions. The above experimental procedures predominantly affected the TCA fraction of cardiac glycogen.

KAYDEN

Hanna, C., McHugo, P. B., and Macmillan, W. H.: Cardiovascular Actions of Histamine and Potassium. Am. J. Physiol. **197**: 1005 (Nov.), 1959.

The cardiovascular actions of intravenous histamine, in doses from 2.5 to 20 μg./Kg. of the free base, were studied in the pentobarbitalized dog by means of the dye-dilution method. With the small dose there was a consistent but small initial increase in cardiac output, and with the larger doses there was a biphasic change in output. Cardiac rate, central venous pressure, central blood volume, hematocrit level, and the mean circulation time were essentially unchanged. Infusions of histamine and of potassium chloride at the rate of 1 μg. and 1 mg./Kg./min., respectively, moderately increased the cardiac output. Potassium chloride had no effect on the arterial blood pressure, cardiac rate, and central venous pressure. Both the infusion of potassium chloride and injection of histamine produced a comparable elevation of the plasma potassium. It is possible that the actions of histamine to increase the plasma potassium contribute to the cardiovascular actions of this amine, especially on the cardiac output.

KAYDEN

Hilton, S. M.: A Peripheral Arterial Conducting Mechanism Underlying Dilatation of the Femoral Artery and Concerned in Functional Vasodilatation in Skeletal Muscle. J. Physiol. **149**: 93 (Dec.), 1959.

A modified volume plethysmograph was used to measure volume changes of the femoral artery in anesthetized cats. Arterial dilatation occurred in response to muscular contractions and also to injections of acetycholine, histamine, and nicotine in the artery distal to the site where the plethysmograph had been applied. Dilatation occurred in denervated preparations and was abolished by the local application of cocaine or by division of the vessel distal to the measuring device. The author concluded that the dilator response was not the result of a spinal reflex or of a circulating substance in the blood stream but rather was mediated by a conducting system which was present locally in the wall of the artery. Various experiments are presented to prove that the conducting pathway is not along any of the known nerve pathways but rather it is suggested that the wave of dilatation is propagated along the smooth-muscle cells of the media. The author concludes that this primitive, peripheral-conducting mechanism is important in the regulation of local blood supply and is independent of central nervous system control.

KARPMAN

Kavaler, F.: Membrane Depolarization as a Cause of Tension Development in Mammalian Ventricular Muscle. Am. J. Physiol. **197**: 968 (Nov.), 1959.

A method was devised that made it possible to depolarize ventricular muscle, over a short interval of length, by applying an external voltage and to record, from the same segment, the developed tension. A fiber bundle, 0.5 to 1.0 mm. in diameter, from the right ventricular cavity of the sheep or calf, was inserted into a close-fitting hole in a plastic block, contained in a Tyrode bath. The fibers were depolarized where they exited from the block. The muscle was held, by suction, at 2 surface points of very small area, 0.4 mm. apart. Measurements with microelectrodes showed that the depolarization was roughly uniform over the length of muscle segment from which tension was recorded. By this means, the action potential (normally lasting about ½ second) could be prolonged to a duration of 2 seconds. This caused tension to be maintained at near-peak levels; relaxation occurred only when the fibers were allowed to repolarize. Evidence was thus adduced in support of the view that the contractile mechanism is continuously responsive to depolarization.

KAYDEN

Mack, R. E., Nolting, D. D., Hogancamp, C. E., and Bing, R. J.: Myocardial Extraction of Rb^{86} in the Rabbit. Am. J. Physiol. **197**: 1175 (Dec.), 1959.

An investigation of the myocardial extraction of Rb^{86} was carried out using the Langendorff preparation in the isolated rabbit heart. Extraction was found to be related exponentially to both the rate of flow and the length of time of the flow. In the determination of coronary blood flow based upon the myocardial uptake of Rb^{86}, an average value for myocardial extraction must be assumed in order to avoid coronary sinus catheterization. The data in these rabbit experiments suggest that when coronary blood flow is increased or decreased 50 per cent the error which results from assuming a constant value for myocardial extraction is of the order of 20 per cent.

KAYDEN

Michal, G., Naegle, S., Danforth, W. H., Ballard, F. B., and Bing, R. J.: Metabolic Changes in Heart Muscle during Anoxia. Am. J. Physiol. **197:** 1147 (Dec.), 1959.

The studies reported deal with the effects of varying periods of complete myocardial anoxia on the concentrations of reduced and oxidized diphosphopyridine nucleotide, reduced and oxidized triphosphopyridine, glycogen, adenosine triphosphate, hexose monophosphate, phosphocreatine, and inorganic phosphorus in heart muscle. Oxygen-lack leads to rapid dephosphorylation of high energy phosphate compounds and to the formation of inorganic phosphorus. The decline of adenosine triphosphate in heart muscle was more rapid than the diminution in the Qo_2 of heart-muscle slices reported previously. There was considerable glycogenolysis. The rate of glycogen breakdown did not appear to depend upon the amount of glycogen present in heart muscle until very low levels were reached. Prior to the onset of anoxia, most of the diphosphopyridine nucleotide was in its oxidized form. This oxidized form of diphosphopyridine nucleotide and reduced triphosphopyridine nucleotide decreased with time, while reduced diphosphopyridine nucleotide increased. The total concentration of diphosphopyridine nucleotides in heart muscle diminished.

KAYDEN

Milton, A. S.: The Enzyme Systems Concerned with Acetylcholine Synthesis in the Atria of the Rabbit Heart. J. Physiol. **149:** 462 (Dec.), 1959.

Acetone-dried preparations of rabbit atria were used to synthesize acetylcholine. This synthesis occurred at a maximal rate when the amount of co-enzyme A was increased. In exhausted atria the acetyl-Co-A-kinase activity was reduced, the rate of acetylcholine synthesis was low, and an increase in synthesis occurred when acetylcholine was added to the incubation mixture; this latter effect occurred only in systems where the generation of acetyl Co-A was dependent on the activity of endogenous enzymes. In the atria, which had ceased to beat, the total amount of acetylcholine was 50 per cent of normal and the bound acetylcholine was reduced to 33 per cent of normal.

KARPMAN

Pieper, H. P.: Adaptation of Cardiac Output to Peripheral Runoff Studied in Intact Dogs. Science **131:** 828 (Mar. 18), 1960.

Twelve experiments were performed on large anesthetized dogs. A specially adapted Howard respiration pump was connected to the abdominal aorta by means of a polyethylene tube inserted through the right femoral artery. This pump was operated so as to cause slow oscillation of the mean arterial pressure by alternately removing and reinjecting blood. Arterial blood pressure was measured through a catheter tip manometer introduced into the aortic arch through the left femoral artery. A catheter tip flow meter was placed in the ascending aorta close to the aortic valves through the left carotid artery. Zero flow in the ascending aorta was obtained by arresting the heart for a few seconds by stimulation of the left vagus nerve. Pressure oscillations were observed not to produce reflex changes in the circulatory system. When the rate of inflow or outflow produced by the pump was altered, any variation of systolic inflow was immediately compensated for by the heart. It was concluded that this mechanism adjusted cardiac output immediately to changes in peripheral outflow. A constant relationship was noted between the systolic inflow and diastolic pressures. This necessarily led to a constancy of the aortic pulse pressure because the vasomotor tone and therefore all other parameters, such as the systolic runoff and the elasticity coefficient of the arterial system, were unchanged by the operation of the pump.

LEVINSON

Richardson, T. Q., and Guyton, A. C.: Effects of Polycythemia and Anemia on Cardiac Output and Other Circulatory Factors. Am. J. Physiol. **197:** 1167 (Dec.), 1959.

Normovolemic anemia and polycythemia were studied in 14 dogs. Cardiac outputs increased with anemia and fell with rises in hematocrit values. Although many factors may play an important role in these variations in cardiac output, there was an indication that viscosity alone may have a major effect. There was no significant association between changes in cardiac output and the following pressures: mean arterial, mean right atrial, mean pulmonary, and mean circulatory. Although the pressures did not change significantly, there was a significant decrease in total peripheral resistance in anemia and a marked rise in polycythemia. It was also found that the maximum number of red cells present for oxygen transport to the tissues was near the mean normal hematocrit level of 40.

KAYDEN

Shepard, J. T., Donald, D. E., Linder, E., and Swan, H. J. C.: Effect of Small Doses of 5-Hydroxytryptamine (Serotonin) on Pulmonary Circulation in the Closed-Chest Dog. Am. J. Physiol. **197:** 963 (Nov.), 1959.

5-Hydroxytryptamine (serotonin) was infused into anesthetized dogs at a rate of 20 μg./Kg./min. In 9 sets of observations on 3 dogs the increase

in the difference of pressure between the pulmonary and the left atrium, which averaged 55 per cent, consistently exceeded the increase in pulmonary blood flow, which averaged 16 per cent. Serotonin therefore is a potent constrictor of pulmonary vessels, even in small concentrations. No changes in the pulmonary artery wedge and pulmonary vein pressures were detected during the infusions of serotonin, nor was there any change in the volume of blood between the pulmonary artery and the root of the aorta. With this dose of serotonin the principal site of the increased resistance to flow through the lungs appeared to be in the precapillary vessels. In the isolated perfused lung, moderate constriction of pulmonary veins also was produced by large doses of serotonin.

KAYDEN

Siebens, A. A., Hoffman, B. F., Cranefield, P. F., and Brooks, C. McC.: Regulation of Contractile Force during Ventricular Arrhythmias. Am. J. Physiol. **197**: 971 (Nov.), 1959.

Causes of fluctuations in ventricular pressure during arrhythmias were studied in anesthetized dogs. Excitability and contractility were measured throughout the cardiac cycle and their relationship to the problem was assessed. The strength of premature contractions was found to vary inversely with prematurity. Weakness of premature beats could not be ascribed to subnormal excitability nor to insufficient ventricular filling. Contractility was virtually zero at the end of the total refractory period, increased progressively thereafter, and was fully restored only at the very end of the cardiac cycle. Sensitivity of contractile force to increments in ventricular filling paralleled the return of contractility. The strength of the postcompensatory contraction was always enhanced, this potentiation increasing as a linear function of the extrasystole's prematurity. Postextrasystolic potentiation was attributed to the extrasystole itself rather than to the pause that followed it or to increases in ventricular filling and distention. It was therefore concluded that pressure fluctuations during ventricular arrhythmias are not due to subnormal excitability and would occur independently of variations in ventricular filling.

KAYDEN

Ulrich, F.: Ion Transport by Heart and Skeletal Muscle Mitochondria. Am. J. Physiol. **197**: 997 (Nov.), 1959.

Isolated mitochondria from rat heart and skeletal muscle were able to maintain concentration gradients of sodium and potassium which were greater at low concentrations of either ion in the incubating medium than at high concentrations. Although the gradient of sodium was not significantly altered by addition of adenine triphosphate and oxidizable substrate to the incubating medium, the mitochondria were able to accumulate increased amounts of potassium by these additions. When the mitochondria were aged by keeping them in suspension at 0-2° C. for 4 or 12 days, the potassium gradient was markedly decreased. Seventy or 80 per cent of the sodium exchanged with Na^{22} in the suspending medium in less than 1 minute and more than 90 per cent of K^{42} had exchanged with mitochondrial potassium at the end of 5 minutes of incubation. Although addition of adenine triphosphate and substrate to the suspending medium had no effect on the turnover of sodium, it appeared to render some of the potassium nonexchangeable. However, by the end of 1 hour approximately 90 per cent of the potassium had exchanged.

KAYDEN

Zoll, P. M., Linenthal, A. J., and Zarsky, L. R. N.: Ventricular Fibrillation: Treatment and Prevention by External Electric Currents. New England J. Med. **262**: 105 (Jan. 21), 1960.

The clinical application of external electric countershock defibrillation (60-cycle alternating current, 0.15 second, 150 to 450 volts) in the treatment of ventricular fibrillation or tachycardia is illustrated by data on 8 patients. Serious recurrent ventricular arrhythmias were successfully terminated in these patients more than 532 times. This same method was also employed approximately 60 times in 9 additional patients. These experiences confirmed the clinical value of external countershock in the termination of ventricular tachycardia and fibrillation and of external electric stimulation in the prevention of these arrhythmias. No significant local, cardiac, or neurologic sequelae could be attributed to electric countershock, even after multiple applications. No untoward incidents occurred in the numerous attending personnel involved in the handling of these patients. Further, since countershock was only administered after the patient had lost consciousness, no pain was suffered from it. Successful external defibrillation required application of the countershock within 4 minutes. This time period could be met, when anticipated, by cardiac monitoring enabling immediate recognition of cardiac arrest and identification of the arrhythmia. It is pointed out that as yet there is no satisfactory pharmacologic approach to the prevention of recurrent ventricular tachycardia and fibrillation with complete heart block. In some such patients these recurrent ventricular arrythmias could be prevented by external electric cardiac stimulation maintained at rates above the basic idioventricular

rate, even though these rhythms could not be terminated, and long-term stimulation proved difficult.

SAGALL

PULMONARY DISEASES

Kabins, S. A., Molina, C., and Katz, L. N.: Pulmonary Vascular Effects of Serotonin (5-OH-Tryptamine) in Dogs: Its Role in Causing Pulmonary Edema. Am. J. Physiol. 197: 955 (Nov.), 1959.

Rapid injection of serotonin (0.5-6.5 mg.) was made into the pulmonary artery in 22 experiments in 12 open-chest anesthetized dogs. Serotonin caused pulmonary arteriolar and venous constriction in the majority of experiments, shown by an increase in the pressure gradients between the pulmonary artery and pulmonary artery wedge pressures, and between the latter and the left atrial pressure, respectively. Three groups of responses were obtained as far as the production of pulmonary edema was concerned. The first group of 3 dogs showed no pulmonary edema. The second group of 3 dogs showed severe bilateral pulmonary edema with left heart failure. The third group of 6 dogs showed moderate to severe bilateral pulmonary edema without evidence of left heart failure. It is suggested that an increase in capillary permeability is responsible, at least in part, for the pulmonary edema found. The similarity of results in the third group to those obtained in the formation of bilateral pulmonary edema following unilateral starch embolization, suggests that serotonin could be an initiating factor in the neurohumoral mechanisms involved.

KAYDEN

Storstein, O., Calabresi, M., Nims, R. G., and Gray, F. D., Jr.: Histamine and Pulmonary Circulation in Man. Yale J. Biol. & Med. 32: 197 (Dec.), 1959.

The circulatory and ventilatory effects of small doses of subcutaneous histamine were studied in 21 patients with chronic pulmonary disease of various types. An average of 0.6 to 0.8 mg. of histamine phosphate was administered to each patient in successive days. On the first day ventilatory function was studied by measurements of vital capacity, maximal breathing capacity, minute breathing volume, and alveolar ventilation. On the following day, after a similar dose of histamine, circulatory changes by means of right-sided cardiac catheterization were studied. Heart rate, systemic, pulmonary artery, and pulmonary wedge pressures, cardiac output, total systemic and pulmonary arterial resistances, arterial oxygen saturation, arterial oxygen tension, alveolar arterial oxygen tension gradient, and respiratory fluctuations in pulmonary artery systolic and diastolic pressures were observed. No consistent bronchoconstriction was noted in the dosage used, so that the circulatory changes could not be consistently related to this mechanism. This would also cast doubt on the role of bronchospasm in patients with asthma as a factor in the production of pulmonary hypertension. The observed circulatory effects of histamine in these patients were increased heart rate and lowered systemic blood pressure. A fall of pulmonary artery pressure and resistance was noted but there was no change in wedge presssure. The degree of change noted could not be correlated with the degree of bronchoconstrictor effect. An increased alveolar-arterial oxygen gradient was noted. This was probably due to alveolar capillary dilatation with alteration of the ventilation perfusion relationship. The findings here do not support broncho-obstructive disease as a mechanism of pulmonary hypertension but do not exclude certain types of bronchoconstriction that could affect pulmonary blood flow or resistance. In the doses used here, subcutaneous histamine will reduce pulmonary artery pressure.

LEVINSON

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Cook, W. F., and Pickering, G. W.: The Location of Renin in the Rabbit Kidney. J. Physiol. 149: 526 (Dec.), 1959.

Magnetic iron oxide was introduced into the glomeruli of the rabbit kidney by infusion through the renal arteries; the kidneys were fragmented and then the magnetic glomeruli were removed with an electromagnet. The magnetic fraction (95 per cent glomeruli) always contained more renin per milligram of nitrogen than the nonmagnetic fraction (95 per cent fragmented tubules). Glomeruli from the outer cortex contained more renin per milligram of nitrogen than glomeruli of the inner cortex and glomeruli with attached tissue fragments contained more renin than the glomeruli without attached tissue fragments. The authors concluded that renin is formed in cells in, or close to, the glomeruli, most likely in the specialized cells of the vascular pole or the epithelial cells of Bowman's capsule and the glomerular capillaries.

KARPMAN

Mehrizi, A., and Hamilton, W. F.: Effect of Levarterenol on Renal Blood Flow and Vascular Volume in Dogs. Am. J. Physiol. 197: 1115 (Nov.), 1959.

T-1824 was injected quickly into the renal artery of dogs and the renal vein stream was divided

into samples every second. From the analysis of these timed samples a dye-concentration curve was plotted and the flow and mean transit time were calculated. Since the flow calculated from the area of this curve agreed closely with the flow measured in the sampling tubes it was assumed that all the injected dye was recovered and that the mean transit time multiplied by the flow equaled the capacity of the active vascular channels. In 7 animals the infusion of levarterenol produced an increase in renal vascular resistance without curtailing renal blood flow to such a degree that the dye curve could not be plotted. In these animals the arterial pressure rose, on the average from 109 to 176 mm. Hg. This change in resistance reduced the renal blood flow from 120 to 84 ml./min., increased the mean transit time from 7.5 to 13.9 seconds and increased the volume of actively flowing blood from 15 to 17 ml. (from 30 to 34 ml./100 Gm. of kidney). From these experiments it is concluded that the classical renal swelling from injection of epinephrine is the result of an increase in the resistance of postcapillary segments of the renal vasculature and a distention of glomerular and possibly of peritubular capillaries. KAYDEN

RHEUMATIC FEVER

Baldwin, J. S., Kerr, J. M., Kuttner, A. G., and Doyle, E. F.: Observations on Rheumatic Nodules Over a 30-Year Period. J. Pediat. **56**: 465 (April), 1960.

The incidence of rheumatic carditis and nodule formation was tabulated for a 30-year period (1928-1958); 948 cases of carditis and 96 patients with nodules were observed. Nodule formation occurred only in patients with active carditis, and the mortality rate was found to be higher in the patient with fewer nodules. The nodules usually occurred after the illness had been present for at least 1 month. The mortality rate was decidedly lower during the second 15-year period but the percentage of episodes of carditis accompanied by nodules was unchanged. The nodules were found to be associated with a more severe and protracted form of rheumatic fever, and the author therefore recommended that the prognosis be guarded and that a vigorous prophylactic regimen be instituted in these patients. KARPMAN

Gilbert, G., David, P., Aerichide, N., and Lefebvre, M.: Treatment and Prevention of Rheumatic Carditis. Canad. M.A.J. **82**: 179 (Jan. 23), 1960.

Eighty-five children aged 3 to 19 years were treated for acute rheumatic fever, and in 46 the attack was the initial one. Forty-one had severe carditis with failure, whereas 44 had moderate carditis with valvular lesions. In each patient treatment consisted of (1) bed rest for 2 to 4 months until all signs of rheumatic activity subsided; (2) penicillin therapy for 10 days because evidence of a recent beta-hemolytic streptococcal infection was found in nearly all cases; (3) prednisone administration in diminishing doses for 6 to 12 weeks in an effort to minimize permanent heart damage. Great improvement was observed in 80 per cent of the children, and 4 per cent died. Substantial lessening of the mitral systolic murmur was noted in 26 of 58 patients although other murmurs persisted. Follow-up examinations for periods of 3 to 4 years disclosed recurrent rheumatism in 9 per cent, despite employment of benzathine penicillin-G prophylactically. It was concluded that corticosteroid therapy in rheumatic carditis was indicated early after onset and for prolonged periods, and that penicillin prophylaxis was of great value in preventing repeated attacks. ROGERS

ROENTGENOLOGY

Bellman, S., Frank, H. A., Lambert, P. B., Littman, D., and Williams, J. A.: Coronary Arteriography. I. Differential Opacification of the Aortic Stream by Catheters of Special Design—Experimental Development. New England J. Med. **262**: 325 (Feb. 18), 1960.

In an attempt to increase the reliability and safety of coronary arteriography the authors have employed a new principle of injection of contrast material. Spiral- and loop-shaped terminations of arterial catheters were utilized, thereby enabling the injection of the contrast material at the periphery of the aortic stream in close proximity to the coronary ostia. With this technic relatively selective opacification of the coronary circulation could be achieved with a smaller amount of contrast substance than was possible by technics aimed at opacifying the entire output of the left ventricle. The development of this new principle and its use in experiments with the dog are described. This principle of selective opacification of the periphery of the blood column should be generally applicable to the study of branches of the aorta or large arteries. SAGALL

Dejar, R., Bergmann, K., Kejar, Z., and Fejfarova, M.: Roentgenologic Differential Diagnosis of Intracavitary Cardiac Thrombi and Tumors. Arch. Kreislaufforsch. **31**: 181 (Dec.), 1959.

The most important angiocardiographic sign of intracavitary cardiac masses is a defect in contrast filling of the cardiac cavity. The authors classify such filling defects, according to their mode of origin, as true filling defects caused by

organic disease of the cavity, pseudo-defects, and defects arising on a functional basis. Illustrations of each of these situations are reported, including myxoma in the left atrium, myxoma in the right atrium, extensive thrombosis of the posterior wall of the left atrium, pseudo-defect because of calcified annulus fibrosus and finally 2 "functional" defects arising from a jet of blood not containing contrast medium, such as blood coming from the inferior vena cava or from an atrial septal defect.

BRACHFELD

Fleischner, F. G.: Unilateral Pulmonary Embolism with Increased Compensatory Circulation Through the Unoccluded Lung. Roentgen Observations. Radiology **73**: 591 (Oct.), 1959.

Although pulmonary embolism is now recognized clinically as well as at autopsy, only recently has the frequency of nonfatal embolism been appreciated. In massive unilateral pulmonary embolism all the pulmonary arterial blood is shunted to the unoccluded lung and the condition may be recognized on a plain roentgenogram. The lung field on the embolized side is more translucent (oligemic lung) while the nonobstructed side shows dilated hilar and peripheral vessels (pleonemia). These changes may be transient during the acute stage of embolism or permanent in the case of permanent massive embolothrombotic obstruction. It is not known whether angiocardiography can be performed with impunity in instances of suspected embolism. It is possible that electrokymography may provide a sensitive tool for the discovery of diminution or absence of pulsation and flow in smaller pulmonary vessels. KITCHELL

Gay, B. B., Jr., and Franch, R. H.: Pulsations in the Pulmonary Arteries as Observed with Roentgenoscopic Image Amplification. Observations in Patients with Isolated Pulmonary Valvular Stenosis. Am. J. Roentgenol. **83**: 335 (Feb.), 1960.

The use of roentgenoscopic image amplification greatly improves the ability to visualize intrinsic pulsations in the pulmonary arterial branches within the lungs. In isolated valvular pulmonary stenosis a characteristic pattern of pulsation is present. The main and left pulmonary arteries reveal a marked increase in intrinsic pulsation, whereas diminution or absence of pulsation of the right descending pulmonary artery branch in the right hilus is seen. These findings are important signs of isolated pulmonary valvular stenosis and should be added to the other well-known clinical and roentgenographic signs. This differential pulsation has not been observed in patients with pulmonary infundibular stenosis. In these patients the heart may be normal in size or slightly enlarged. The main and left pulmnary arteries are dilated, and the peripheral pulmonary arterial branches and pulmonary veins are usually normal.

KITCHELL

Hettler, M.: Angiographic Problems and Possibilities. Fortschr. Rôentgenstr. **92**: 97 (Jan.), 1960.

During rapid injection of contrast medium, movement of the syringe can easily cause the cannula to slip out of the artery, resulting in an extravasate; this can be prevented by inserting a long flexible tube between syringe and needle, once the latter is well inserted into the artery. This method also prevents roentgen exposure of the operator's hands. The cannula developed by the author contains a mandrin provided with a flexible steel spiral at its end; when emergence of blood indicates that the cannula has penetrated the arterial wall, the mandrin is inserted into the cannula and allows easy introduction of the cannula along the arterial lumen. For arterial catheterization the author uses a longer cannula of the same type, provided with an outer cannula half as long; the outer cannula is pushed through skin and into the artery over the inner cannula only after the latter has been well inserted into the arterial lumen. This prevents the hematomas that often occur with a long outer cannula, which must be pushed through the skin while the inner cannula is not yet firmly lodged in the artery. Use of the double cannula results in a smaller incision in the arterial wall than if a single wide cannula is used. The author also describes a stand carrying an inflatable rubber pelotte, which permits easier compression of the artery after puncture; the pressure inside the pelotte is adjusted according to the blood pressure of the patient and gradually reduced during the following 5 or 6 hours. Use of these refinements practically eliminates incidents, so that arterial puncture and catheterization can be used by all radiologists. LEPESCHKIN

Jacobson, H. G., and Shapiro, J. H.: Simultaneous Biplane Large-Film Serialography in Cerebral Angiography. 82: 773 (Nov.), 1959.

The utilization, including technical details, of the biplane Schönander unit in cerebral angiography is described. There are both advantages and disadvantages to this method of examination but it is felt that the technic is capable of producing optimal results. KITCHELL

Laboux, Dupon, Cornet, and Horeau: Coronary Venous Injection under High Pressure during Angiocardiography (Evolution of Electrocardiographic Disturbances. Arch. mal. coeur **12**: 1347 (Dec.), 1959.

In a 13-year-old boy with aortic coaretation,

angiocardiography was performed under general anesthesia, 60 ml. of iodated contrast medium being injected rapidly under high pressure. During injection complete atrioventricular dissociation appeared, and the radiograph showed that the medium had been injected into the coronary venous sinus and had collected in the supradiaphragmatic epicardial region. In addition to right bundle-branch block, which was present before angiocardiography, the electrocardiogram showed deep inversion of the T waves in leads V_3 and V_4, which remained unchanged for 3 weeks. At this time the coarctation was corrected surgically with good results, but after 12 hours shock developed, which was controlled by blood transfusion. During shock all abnormalities of the T wave disappeared, and had not returned at the time the patient was discharged.

LEPESCHKIN

Lewitan, A., and Kroop, I. G.: Experience with Two New Media in Angiocardiography. A Preliminary Report. 82: 779 (Nov.), 1959.

Two new, water-soluble contrast agents, cardiografin 85 per cent and cardiografin 90.5 per cent, have been employed in roentgenographic studies in 29 patients. The 85-per cent solution proved to have great diagnostic value in congenital cardiac lesions in children. This was also used in the study of pulmonary lesions in adults and here there was satisfactory to excellent opacification of the entire cardiovascular system, including the left ventricle and the aorta. Cardiografin, 90.5 per cent, provided better contrast where large left-to-right shunts were present with dilution of the contrast medium. The lower viscosity of cardiografin, 85 per cent, and its higher solubility at room temperature made for smoother technic and more satisfactory results. No serious side reactions were seen in the entire series and only 1 patient required the administration of epinephrine because of the development of a generalized urticaria. This study suggests that the cardiografins are highly satisfactory media for use in angiocardiographic and other intravenous roentgenographic procedures in both children and adults.

KITCHELL

Porstmann, W., and Kokkalis, P.: Problems of Coronary Arteriography. Fortschr. Röntgenstr. 6: 690, 1959.

For the exact localization of a coronary stenosis or occlusion, coronary arteriography cannot be replaced by any other diagnostic method. This localization is necessary for coronary endarterectomy or for anastomosis of an extracardiac artery to a coronary artery distal to the occlusion. Injection of dye through an aortic catheter during acetyl choline standstill allows perfect visualization of even the finest coronary branches, especially if a small focal spot is used, but the 10 to 30 ml. of dye necessary for this purpose caused severe cerebral reactions in 3 of 22 dogs. If a double-lumen catheter was used and the aorta distal to the coronary ostia was occluded by means of a rubber balloon filled with carbon dioxide, only 6 to 10 ml. of dye were necessary, and cerebral reactions could be avoided. The disadvantage of this method is that at present the balloon can be introduced only through the larger arteries (femoral, carotid, or brachial) and requires suture. Application of this method to patients with coronary disease depends on definite confirmation that acetyl choline asystole is free of danger, and on development of contrast media causing less myocardial irritation than the triiodinated substances currently in use.

LEPESCHKIN

Steinberg, I.: Dilatation of the Aortic Sinuses in the Marfan Syndrome: Roentgen Findings in Five New Cases. Am. J. Roentgenol. 83: 302 (Feb.), 1960.

Angiocardiography has made possible the diagnosis of aneurysmal dilatation of the aortic sinuses in Marfan's syndrome during life. Ten patients with dilatation of the aortic sinuses in Marfan's syndrome have been studied at this center. Five of these were new cases not previously reported. Dilatation of the aortic sinuses is common in Marfan's syndrome and 9 patients were shown to have this condition. In 1 it was aneurysmal and associated with huge dilatation of the ascending aorta. Angiocardiography revealed the cardiovascular abnormality and in some instances provided the clue that linked the associated skeletal and ocular deformities. Marfan's syndrome is not as rare as previously supposed, and the radiologist by noting the unusually long and thin extremities (especially the fingers and toes), thoracic deformities, and cardiovascular abnormalities may be the first to suggest the diagnosis. The form fruste type of Marfan's syndrome should be kept in mind whenever there is aneurysmal dilatation of the aortic sinuses or ascending aorta.

KITCHELL

Steinberg, I., Finby, N., and Evans, J. A.: A Safe and Practical Intravenous Method for Abdominal Aortography, Peripheral Arteriography, and Cerebral Angiography. Am. J. Roentgenol. 82: 758 (Nov.), 1959.

The advantages of securing abdominal aortography, peripheral arteriography, and cerebral

angiography by intravenous injection are obvious. This method has distinct advantages over the translumbar, carotid, and vertebral arterial injection routes that have sometimes been associated with serious complications and occasionally death. The injection is made rapidly and simultaneously into both arms with special syringes attached to Robb-Steinberg cannulas, with use of concentrated organic iodide at 1 ml. per Kg. of body weight. Conventional roentgen equipment is all that is required. Aneurysmal and occlusive disease of the abdominal aorta and its branches can be readily diagnosed, this is also true for cerebral angiography especially when biplane studies are made. The exposures are timed by first determining the arm-to-tongue circulation time with injections of sodium dehydrocholate.

KITCHELL

SURGERY AND CARDIOVASCULAR DISEASE

Baronofsky, I. D., Steinfeld, L., Kreel, I., Gordon, A. J., and Grishman, A.: Congenital Aortic Stenosis: Diagnosis and Surgical Treatment. New York State J. Med. **59**: 4349 (Dec.) 1959.

Congenital aortic stenosis consists of a membrane with fused commissures of fibrous material. Therefore, simple dilatation is insufficient, since the diaphragm of this aortic valve will merely rebound against the dilator. Furthermore, if there is evidence of subvalvular stenosis, this pathology too must be corrected. These procedures are best accomplished with the use of hypothermia and the pump oxygenator—as well as cardiac arrest. Early operation is indicated in patients who are symptomatic or who have a pressure gradient of about 50 mm. Hg between the left ventricle and the aorta. Usually the left ventricle is enlarged. The presence of valvular calcification does not influence the need for surgery. The authors prefer percutaneous puncture of the left ventricle to obtain the pressure gradient preoperatively and demonstrate that this gradient can be obliterated by successful surgery.

KRAUSE

Clowes, G. H. A., Jr., Alichniewicz, A., Del Guericio, L. R. M., and Gillespie, D.: The Relationship of Postoperative Acidosis to Pulmonary and Cardiovascular Function. J. Thoracic Surg. **39**: 1 (Jan.), 1960.

Forty-five patients were selected at random. These underwent pneumonectomy, lobectomy, and thoracotomy for operations on structures other than the lung. The purpose of this paper was to study circulatory and respiratory responses occurring during and in the first week after the surgical procedure. A comparison was made between patients exhibiting normal responses and those exhibiting hypotension at various times during the recovery period. These studies suggested that prolonged acidosis associated with uncorrected hypoxia leads to sudden death from circulatory collapse. Of the 45 patients, 5 died subsequent to the operation and 3 others had hypotension relieved by correction of respiratory inadequacy. Of the 5 patients who died, 4 had undergone pneumonectomy and 1 a lobectomy. Patients were studied with measurement of cardiac output, venous pressure, determinations of pulmonary function, and analysis of the blood gases, blood electrolytes, and pH. Determinations were made preoperatively, following intubation and during induction of anesthesia, near the completion of the surgical procedure, early in the postoperative period, on the morning of the first day postoperatively, the second day, the third or fourth day, and after 1 week. Cardiac output fell with induction of anesthesia and, early in the operation, dropped further toward the end of the operation, but rose again later. Vena caval pressure rose with induction of anesthesia. It remained elevated until removal of the intubation. Cardiac output became elevated at this time. The blood pressure and pulse rate in those who died were different from those of the survivors only 2 or 3 days before death. At those times there was a significant fall in blood pressure and rise in pulse rate. The patients who died showed no statistically significant difference in respiration from the survivors. Twenty-one of the patients had acidosis during the course of the thoracotomy and in each case it was related to carbon dioxide retention. Oxygen saturation was more uniformly depressed following lobectomy than pneumonectomy. Significant serum sodium reduction was most pronounced the afternoon of the operation and the following day. Lactate was elevated, particularly in those who were hypoxic or hypotensive. Circulatory failure was the chief hazard and was usually preceded by severe respiratory abnormalities. It appeared that the common factor resulting from the respiratory inadequacy was a prolonged period of progressively increasing acidosis and moderate to severe hypoxia. As noted in 1 patient, a short period of intense respiratory acidosis was not lethal. It would appear that the presence of acidosis limited the ability to compensate for even moderate degrees of hypoxia in the relatively acute state. Therapeutically the important points were the prevention and correction of prolonged acidosis as well as maintenance of normal oxygen tensions.

LEVINSON

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York
Telephone Gramercy 7-9170

Abstracts of Papers Due May 15 for 1961 AHA Scientific Sessions

Official application forms are now available for the submission of abstracts of papers to be presented at the annual Scientific Sessions of the American Heart Association in Bal Harbour, Florida, October 20-22, 1961. *The deadline for submitting abstracts is May 15, 1961.*

Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and include a brief digest of the results obtained and conclusions reached. All applications will be screened by the Committee on Scientific Sessions Program of the American Heart Association.

Official forms for submitting abstracts of papers may be obtained from Richard E. Hurley, M.D., Medical Associate, American Heart Association, 44 East 23rd Street, New York 10, New York. Applications for space for *scientific exhibits*, which must be returned postmarked not later than May 15, 1961, may also be obtained from Dr. Hurley.

Space for *industrial exhibits* may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, New York.

Arteriosclerosis Council Meeting Set; Deadline for Abstracts is May 15

The AHA Council on Arteriosclerosis—American Society for the Study of Arteriosclerosis—will hold its 15th Annual Meeting from Wednesday through Friday, October 18-20, 1961, immediately preceding the American Heart Association's annual Scientific Sessions at Bal Harbour, Miami Beach, Florida.

May 15, 1961, has been set as the deadline for submitting abstracts of papers for presentation at the Council sessions. Official application forms for submitting abstracts, not to exceed 250 words, may be obtained from Jeremiah Stamler, M.D., Chicago Board of Health, 54 West Hubbard Street, Chicago 10, Illinois. Forms may also be obtained from the American Heart Association, 44 East 23rd Street, New York 10, New York.

Sessions of the Council meeting will be open to all interested individuals whether or not they are Council members. Abstracts of papers for presentation also are invited from members and non-members alike.

Readers Reminded to Renew 1961 Subscriptions

Readers of *Circulation* and *Circulation Research* are urged to renew their subscriptions now for 1961 through the Publishing Office, American Heart Association, 44 East 23rd Street, New York 10, New York.

Annual subscription rates are: *Circulation* (12 issues), $14 in the U.S. and Canada, $15 elsewhere. *Circulation Research* (6 issues), $9 in the U.S. and Canada, $10 elsewhere. (Special annual rate for full-time research fellows, $7.) Combined subscription to both journals, $21 in the U.S. and Canada, $23 elsewhere.

Interns, residents and medical students may subscribe to the journals at reduced rates this year for the first time. These are: *Circulation*, $9; *Circulation Research*, $6; or $15 for both publications (U.S. and Canada only).

Association's 8 Councils Elect New Officers

New officers of the American Heart Association's eight Councils have been elected as follows:

Council on Arteriosclerosis: Aaron Kellner, M.D., New York, Chairman; Campbell Moses, Jr., M.D., Pittsburgh, Vice Chairman.

Council on Basic Science: Gordon K. Moe, M.D., Syracuse, New York, Chairman; Lysle H. Peterson, M.D., Philadelphia, Vice Chairman.

Council on Cardiovascular Surgery: William W. L. Glenn, M.D., New Haven, Connecticut, Chairman; Harris B. Shumacker, Jr., M.D., Indianapolis, Vice Chairman.

Council on Circulation: Kenneth Kohlstaedt, M.D., Indianapolis, Chairman; Howard Burchell, M.D., Rochester, Minnesota, Vice Chairman.

Council on Clinical Cardiology: Wright R. Adams, M.D., Chicago, Chairman; Lewis E. January, M.D., Iowa City, Iowa, Vice Chairman.

Council on Community Service and Education: Herbert Pollack, M.D., New York, Chairman; John G. Smith, M.D., Rocky Mount, North Carolina, Vice Chairman.

Council for High Blood Pressure Research: James T. Griffin, Cleveland, re-elected President; Milton Mendlowitz, M.D., New York, Chairman, Medical Advisory Board.

Council on Rheumatic Fever and Congenital Heart Disease: James W. DuShane, M.D., Rochester, Minnesota, re-elected Chairman; Katharine D. Brownell, M.D., New York, re-elected Vice Chairman.

Physicians, Lay Leaders Honored by Association

Awards of Merit for distinguished service in the development of the program of the American Heart Association were presented to three physicians and three lay leaders at a meeting of the Association's Board of Directors in December. Two physicians were also cited for distinguished service to the AHA Research Committee.

Recipients of the Award of Merit were:

Mrs. Schroeder Burnham, Greenwich, Connecticut; A. Wilbur Duryee, M.D., New York; Howard P. Lewis, M.D., Portland, Oregon; H. Willis Nichols, Cincinnati; John G. Smith, M.D., Rocky Mount, North Carolina; and Ray B. Wiser, San Francisco.

Members of the Research Committee who received citations were:

Charles H. Rammelkamp, Jr., M.D., Cleveland, who completed six years of service to the Committee, including 18 months as Chairman; and Franklin D. Johnston, M.D., Ann Arbor, who served the Committee for five years, including 18 months as Vice Chairman.

Volumes on Diuretics, Smoking, Published by Sciences Academy

The New York Academy of Sciences has published a 249-page monograph on "New Diuretics and Antihypertensive Agents" which constitutes "the latest and most definitive outline of the mechanisms of action and therapeutic application of the chlorothiazide, phthalimidine and antialdosterone drugs." According to the Academy's announcement, "these nonmercurial, orally effective, highly potent and well-tolerated diuretic drugs have revolutionized the treatment of disorders of congestive failure and now constitute the primary form of drug therapy for the management of hypertension, in the treatment of which drastic salt restriction has been rendered obsolete." The volume, Number 88, is priced at $3.50 a copy.

The Academy has also announced publication of a 344-page monograph on "Cardiovascular Effects of Nicotine and Smoking," by Carl J. Wiggers, M.D., *et al.*, listed as volume 90, at $4.00 a copy. Both volumes are obtainable from The New York Academy of Sciences, 2 East 63rd Street, New York 21, New York.

Meetings Calendar

March 6-9: American College of Surgeons, Sectional Meeting, Philadelphia. William E. Adams, 40 E. Erie St., Chicago 11, Illinois.

March 13-16: National Health Council, New York. Philip E. Ryan, 1790 Broadway, New York 19, New York.

March 20-24: American Surgical Association, Boca Raton, Florida. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 10-14: American Physiological Society, Atlantic City. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D.C.

April 17-20: American Academy of General Practice, Miami Beach. Mac F. Cahal, Volker at Brookside, Kansas City 12, Missouri.

April 24-26: American Association for Thoracic Surgery, Philadelphia. Miss Ada Harvey, 7730 Carondelet Ave., St. Louis 5, Missouri.

April 28-30: American Psychosomatic Society, Atlantic City. Morton F. Reiser, 265 Nassau Rd., Roosevelt, New York.

April 30: American Federation for Clinical Research, Atlantic City. James E. Bryan, 250 W. 57th St., New York 19, New York.

May 2-3: Association of American Physicians, Atlantic City. Paul Beeson, Yale University School of Medicine, New Haven 11, Connecticut.

May 5-7: American Society of Internal Medicine, Miami Beach. G. T. Bates, 350 Post St., San Francisco 8, California.

May 7-11: International College of Surgeons, North American Federation, Annual Congress, Chicago. H. E. Turner, 1516 Lake Shore Dr., Chicago 11, Illinois.

May 8-12: American College of Physicians, Miami Beach. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Ave., New York 1, New York.

May 31-June 2: Canadian Federation of Biological Societies, Ontario. E. H. Bensley, 1650 Cedar Ave., Montreal 25, Canada.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois.

June 25: Society for Vascular Surgery, New York. George H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Maryland.

June 26-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

July 1-4: International College of Surgeons, New England Regional Meeting, Cape Cod, Massachusetts. M. L. Brodny, 4646 N. Marine Dr., Chicago 40, Illinois.

August 7-10: National Medical Association, New York. John T. Givens, 1108 Church St., Norfolk, Virginia.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 20-24: American Heart Association, Annual Meeting and Scientific Sessions (October 20-22), Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

Abroad

March 17-19: International Medical Conference, Liege, Belgium. Secretariat, Castellezgasse 35, Vienna 11, Austria.

June 2-5: Latin-American Congress of Physical Medicine, Lisbon. C. L. deVictoria, 245 E. 17th St., New York, New York.

June 3-15: International Medical-Surgical Meetings, Turin, Italy. Minerva Medica, Corao Bramante, Turin.

August 22-25: International Pharmacological Meeting (First), Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 10-15: International Neurological Congress, Rome. G. Alema, Viale Universita, 30 Rome, Italy.

1962

October: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 300, Mexico, D.F.

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